COLLAGEN DISEASES

COLLAGEN DISEASES

—Including—

SYSTEMIC LUPUS ERYTHEMATOSUS • POLYARTERITIS
DERMATOMYOSITIS • SYSTEMIC SCLERODERMA
THROMBOTIC THROMBOCYTOPENIC PURPURA

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TO

ARLIE V BOCK

D BRUCE DILL

and the late

LAWRENCE J HENDERSON

Physician, Physiologist and Philosopher, respectively In spite of a great difference in personality, each one was to me an outstanding individual, a fine teacher and an ever-loyal friend

JHT

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Preface

However other writers of monographs in medicine may proceed, in my own case the Preface, always prepared last, marks a pleasant cessation of labors With more satisfaction than probably is warranted, I turn to the compilation of an index and eventually to proofreading, the culmination of twenty years of sporadic awareness of the need for a concise monograph on the disorders described herein, and the final result of eighteen months of reference work, writing and rewriting

Twenty years of sporadic awareness refers to a brief exchange of correspondence with the late Dr Campbell P Howard, one-time pupil of William Osler in Baltimore, when he was Professor of Medicine in McGill University at the peak of his professional career It was my privilege to feel the warmth of the personality of "C.P H " only through his written words, but I can vouch for his eminence as a teacher and clinician while entrusted with the Department of Medicine at the University of Iowa, only a few miles by dirt road from my birthplace Although the correspondence began in 1936, the origin of a common interest may be traced to the preceding year, when, at the age of sixty, Dr Howard, upon recognizing for the first time a case of scleroderma with calcinosis, described his feelings as follows· "To a student of medicine a new clinical experience always gives a thrill Even the most blasé hospital physician is learning something new each day though he may not be prepared to admit it, certainly at least once a month he is faced by some problem that has not confronted him before Such was my position early in January, when on making my daily ward visit, I was

shown this patient whose case report I am about to relate; I realized that the condition was a new one to me"

The quotation above is an excerpt from the introductory paragraph to a paper presented in 1935 before the Association of American Physicians* entitled, "A Case of Early Scleroderma with Calcinosis." It should be noted also that before the same scientific assembly Dr. George Baehr presented a communication entitled, "A Diffuse Disease of the Peripheral Circulation (Usually Associated with Lupus Erythematosus and Endocarditis)." No discussion followed Dr. Howard's presentation, but several queries were addressed to Dr Baehr. Dr Joseph H. Pratt of Boston, inquired: "I wish Dr Baehr would tell us if he is able to make the diagnosis of the disease [lupus] in the absence of skin lesions If so, I am especially interested to know how he would distinguish it from rheumatoid arthritis" Several comments were made by Dr Emanuel Libman of New York, who displayed a great interest in this communication.

Thus far in the Preface, scleroderma and lupus erythematosus have been introduced as well as the difficulty encountered at times in distinguishing lupus from rheumatoid arthritis Dr. Howard used the term, "scleroderma with calcinosis" to describe his case, but he might have committed an error similar to mine, in describing a case of "dermatomyositis with scleroderma and calcinosis . . ,"[*372*] because the differentiation between dermatomyositis and scleroderma, in patients with calcinosis, has not been defined clearly Yet one other "collagen disorder" had attracted the interest of Dr Howard a decade earlier He reviewed the literature on periarteritis nodosa in 1925 [*216*] at the same time that Moschowitz [*579*] described a case of thrombotic thrombocytopenic purpura

At the time of his death in 1936 Dr. Howard had prepared a fine bibliography on the subject of calcinosis, which supplemented in some instances and duplicated in others, a similar project that I had undertaken Only a modicum of

* Transactions of the Association of American Physician, vol 50, 1935

progress could be documented before World War II brought an effective halt to my efforts Following the war, the increasing incidence of several "rare" collagen disorders was directly responsible for the cessation of daydreaming about the preparation of the manuscript and for the stimulus to start working upon it The results constitute the chapters that follow on Systemic Lupus Erythematosus, Polyarteritis, Dermatomyositis, Systemic Scleroderma and Thrombotic Thrombocytopenic Purpura

It is always a pleasure to acknowledge assistance from persons and institutions who have lent a helping hand Many times also the recipients of this acknowledgment are pleased to be so recognized I have even assumed at times that institutions, such as hospitals and medical schools, cold impersonal structures on the outside, may derive some inward sense of appreciation when they are the object of acknowledgment

Dr Ricardo Ferrandis, a Castilian, studying in America and currently a Training Fellow in Arthritis, helped tremendously in the library work Somewhat more than five times as many articles were read as are listed in the bibliography In most instances decision regarding acceptance or rejection was made after each of us had scanned the original one or more times But Dr Ferrandis' work on the manuscript is not over He has already begun to translate it into Spanish for the Latin American countries I believe that as North Americans we are charged with the responsibility of helping, whenever we are able, to exchange suitable medical information with our associates South of the Border I hope this, the latest of several efforts on my part to do so, will not be the last

The pathologic material was made available by my colleagues, Drs Kornel Terplan and Dorothy Shaver in the Department of Pathology, and Drs Stuart Vaughan, Raymond Kibler and Miss Jeanette Corbett in the Department of Clinical Pathology The excellence of the roentgenography is due to the interest of Dr Gordon Culver of the Department

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SYSTEMIC LUPUS ERYTHEMATOUS

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PLATE I.—Butterfly rash on the face of a patient with SLE



PLATE II.—Section of a kidney from a patient who died from SLE. There is proliferation of endothelial cells of the glomerular capillaries and hyaline thickening of the basement membrane which creates the "wire-loop" appearance × 96



PLATE III.—Section of the epicardium from a patient who died from SLE. The epicardium is thickened with fibrinoid degeneration surrounding the vein. Masson Trichrome stain × 96.



PLATE IV.—LE cells in the buffy coat of a patient with SLE. Wright's stain × 1000.

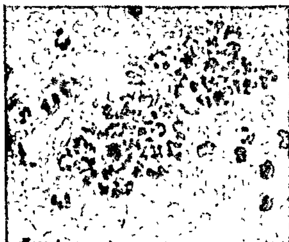


PLATE V—LE rosettes in the buffy coat of a patient with SLE Wright's stain × 450



PLATE VI—Section of a muscle removed at biopsy from a patient with polyarteritis There is acute fibrinoid necrosis of the media in an arteriole surrounded by dense cellular infiltration The inflammation extends between the adjoining muscle bundles × 96



PLATE VII.—Section of a muscle from a patient who died from polyarteritis There is a small aneurysmal bulge of the artery with chronic changes. These consist of eccentric endarteritic proliferation and fibrosis with scattered round cell infiltration in the adventitia. × 96.



PLATE VIII.—Section of a muscle from a patient who died from polyarteritis Chronic changes in the arterioles consist of irregular narrowing of the lumen, fibrosis of the intima and extensive fibrosis of the adventitia Except for a small segment, the media is well preserved × 96.



PLATE IX.—Rash and edema of the face of a patient who had suffered from acute dermatomyositis for eighteen months. The patient died three years after onset of clinical symptoms.



PLATE X.—Section of striated muscle from a patient who died from acute dermatomyositis. There are chronic inflammatory changes with edema and fibrosis. There are numerous atrophic muscle fi[illegible] and a few dark pink staining muscle fibers with evidence of degeneration. × 96



PLATE XI.—Section of skin removed at biopsy from a patient with acute dermatomyositis. There are chronic inflammatory changes in the cutis, particularly about one arteriole. × 96



PLATE XII.—Advanced cutaneous changes on the face of a patient with chronic systemic scleroderma. Symptoms had been present for more than 10 years.

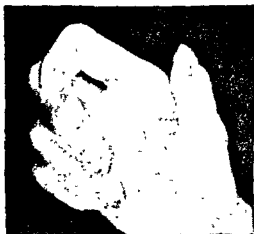


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PLATE XIV.—Section of skin removed at biopsy from a patient with chronic systemic scleroderma. *There is a uniform increase in collagen fibers throughout the cutis.* The papillary bodies are obliterated. × 96



PLATE XV—Section of striated muscle from a patient who died from chronic systemic scleroderma There is atrophy of the muscle fibers, and fragmentation and edema of the fat cells. There is minimal lymphocytic inflammatory reaction. × 96

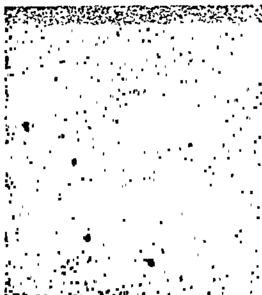


PLATE XVI—Section of a lymph node from a patient with TTP. The hyaline thickening beneath the endothelium has almost occluded the lumen of the blood vessel × 96

Introduction

INCREASED PROMINENCE has been given during the past decade to those morbid states associated with a dysfunction of connective tissue. Rheumatoid arthritis and acute rheumatic fever are included in this category of collagen diseases as well as the less common maladies, systemic lupus erythematosus (acute disseminated lupus erythematosus), polyarteritis (periarteritis nodosa), dermatomyositis, systemic scleroderma (generalized scleroderma), and thrombotic thrombocytopenic purpura, respectively. There are several reasons for the increased prominence of this miscellany of disorders. First, the etiology of the pathologic lesion is unknown in each instance, although there is a strong presumption concerning the causative mechanism in polyarteritis. Obviously the unknown in medical science presents a challenge to the physician at the bedside as well as to the investigator in the clinical and basic science laboratories.

Secondly, the less common collagen disorders have enjoyed an abundance of popularity that usually accompanies the discovery of any "new" disease. While the objection may be raised that these maladies are not new in medical literature, actually they are new to many physicians. Thirdly, the resurgence of curiosity concerning the disorders of muscles and joints, i.e., arthritis, may be attributed partially to the development of new and startling therapeutic agents in recent years which, in turn, contribute to the tremendous interest generated in the less common collagen disorders together with the more familiar ones.

Lastly, physicians have recognized an increased incidence during the past few decades of each of the less common

disorders of connective tissue without a concomitant increase in the more usual maladies. Before the second world war many of us were scarcely aware of the existence of any of the maladies in the first group, and those who read of these rare conditions or had seen isolated examples of one or more of these entities were in the minority. The lack of appreciation of the existence as well as the lack of appreciation of the clinical manifestations of the several conditions has changed rapidly during the past decade with the apparent increase in incidence and the factual increase in recognition These dyscrasias are no longer oddities, for it is not unusual to find several patients afflicted with one or the other of the unusual collagen diseases in a contemporary census of any large general hospital.

The introduction of the term "diffuse collagen disease" into clinical medicine is accredited to Klemperer, Pollack and Baehr [*444*], who applied it to acute disseminated lupus erythematosus, to generalized scleroderma in 1942, and later to dermatomyositis The term was employed originally by these investigators to emphasize the concept that the diseases were associated with injury to a tissue widely distributed throughout the body, i e, connective tissue No implications were made concerning specificity or a common etiology. Unfortunately this original concept has been sadly abused as expressed by Klemperer [*86*], as follows: " . . the impatience of clinical investigators and a peculiar worship of diagnostic terms had led to an exaggerated popularity of the diagnosis collagen disease There is danger that it may become a catch-all term for maladies with puzzling clinical and anatomical features " In spite of these misgivings, the term collagen disorder serves a useful purpose in focusing attention upon a *collection of diseases that defy an understanding of* their pathogenesis and permit only partial alleviation of symptoms

The classification employed for the more common as well as for the less common maladies that are pertinent to this monograph is generally accepted despite several vehe-

ment objectors Probably the term "rheumatoid arthritis" should be mentioned first, even though it will be treated somewhat briefly The diagnosis of rheumatoid arthritis in many patients is founded upon clinical findings only, since no conclusive laboratory tests or procedures are available to confirm the clinical presumption prior to the development of chronic deforming changes in the joints Certain features in the clinical history, physical findings and laboratory examination point the way to a presumptive diagnosis of rheumatoid arthritis in a well-developed case A majority of physicians interested in rheumatism and arthritis would concur in the interpretation of the data in such an instance But what is atypical rheumatoid arthritis? Some patients with "typical" rheumatoid arthritis subsequently present clinical and pathologic evidence of systemic lupus erythematosus or of systemic scleroderma In retrospect, possibly the initial morbid development should have been labeled something else than typical rheumatoid arthritis from the very onset of symptoms Obviously, it is not possible, with the diagnostic armamentarium currently available, to determine whether typical or atypical rheumatoid arthritis is but a forerunner of the unusual collagen disorder when such a transformation occurs Hence, the term rheumatoid arthritis, when used in this discussion, will refer only to the entity that manifests itself clinically as joint disease of the garden-variety type Prognosis concerning the ultimate course usually is associated with uncertainty, as may also be the case in regard to acute heumatic fever

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE), the first of the nsual collagen disorders to be discussed in a comprehensive hion, does not always present clinical findings that are dily recognized and that point specifically to this general- disorder The malady represents a transition in some nts from chronic discoid lupus, a benign process so long remains localized. SLE develops in other patients after d of one or more years of symptoms highly suggestive cal rheumatoid arthritis as noted above SLE may also

be responsible for one or more episodes of what appears to be the usual variety of acute rheumatic fever.

The term POLYARTERITIS has been selected in preference to periarteritis nodosa. Elimination of "nodosa" has been recommended because nodular lesions are detected infrequently upon physical examination, particularly in the early stages of the disease. The presence of palpable nodules along the great vessels, therefore, should not be included as one of the vital diagnostic criteria. Another confusing item concerns the variations of polyarteritis which may be recognized clinically in selected instances and segregated by the pathologic findings Emphasis will be placed in this presentation upon the composite clinical picture rather than upon detailed differentiation of the subtypes. There are well documented instances of the lesions of polyarteritis remaining localized and relatively asymptomatic for several years When the vascular lesions are disseminated, the disease usually advances rapidly to a fatal termination.

DERMATOMYOSITIS is a diffuse, musculocutaneous process that may be recognized as a distinct clinical entity in most patients at the time of initial appearance of symptoms The diagnosis is established at other times after a prolonged course of joint and muscle distress, with or without permanent joint damage Mimicry of acute rheumatic fever likewise has been observed If dermatomyositis progresses, as it does in most patients, acute or subacute symptoms persist until death. A few of those afflicted may live for several years; the pathologic changes meanwhile may gradually metamorphose. This results in a clinical state usually indistinguishable from chronic systemic scleroderma

Localized SCLERODERMA will be discussed only casually in this review So long as scleroderma remains localized and confined to the hands or face, it is a relatively benign process When the lesions become diffuse, acute or subacute systemic symptoms develop that warrant serious attention. Generalized scleroderma may persist in the acute stage until death If the acute process subsides, unremitting changes appear

eventually, and chronic systemic scleroderma, usually indistinguishable from the late stages of dermatomyositis, results

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) is the last dyscrasia that will be presented in this discussion of collagen disorders This condition, first described more than two decades ago, was believed by some to be a variant of idiopathic thrombocytopenic purpura The endothelial proliferations in the blood vessels in this malady were assumed to be thrombi, although the specific lesion possessed the staining characteristics of collagen Another feature implying a relationship of TTP to the four conditions just enumerated is suggested from the etiologic mechanism, i e , hypersensitivity

An undercurrent of skepticism prevailed throughout the formulation of this classification by the writers Clinically, the individual maladies under consideration claim a relatively complete and distinctive assemblage of features adequate to warrant an unequivocal diagnosis if the patient is followed for a sufficient length of time A sufficient length of time in some cases may comprise a post-mortem examination Variants or subtypes of each of the conditions have been described but will not be emphasized in this presentation At the risk of this classification becoming obsolete at some future time, it will be retained because it is believed that it serves a useful purpose in current nosography

Several other maladies might have been discussed if this monograph were encyclopedic or even exhaustive in scope Serum sickness, Loeffler's pneumonia, thromboangiitis obliterans, ulcerative colitis, glomerulonephritis, blood group incompatibility, malignant hypertension, erythema nodosum, erythema multiforme, pemphigus and anaphylactoid purpura have been classed by some investigators as collagen disorders also We have thought it prudent to omit any detailed discussion of these maladies, and will confine our attention to the diffuse disorders with a grave prognosis as a group

The relationship of the rarer collagen disorders to rheumatoid arthritis and to acute rheumatic fever merits addi-

tional comment In the initial weeks or months of the clinical course of each of the first four less common dyscrasias, a *presumptive* diagnosis of acute rheumatic fever or acute rheumatoid arthritis may appear justified and substantiated by sound clinical data Pertinent evidence that constitutes the basis of this presumption is not difficult to find. Fever, malaise, arthralgia and myalgia are initial complaints common to the more typical rheumatic conditions Since acute rheumatic fever and acute rheumatoid arthritis are diagnoses based upon clinical findings, the opportunity for overlooking the possibility of one of the unusual collagen disorders is not unique Some patients who appear to have satisfied all or most of the clinical criteria for a diagnosis of acute rheumatic fever or acute rheumatoid arthritis, at some future time lose the features exclusively of these maladies and present evidence of unmistakable systemic lupus erythematosus, polyarteritis, dermatomyositis or scleroderma It is not possible at this stage of our knowledge to determine whether or not the unusual collagen disorder was present from the beginning of symptoms or whether the morbid process was acute rheumatoid arthritis originally, and subsequently changed into one of the unusual disorders. We believe that the former explanation is valid in most instances Another point in common between the usual and the unusual collagen disorders is the symptomatic response, usually temporary to be sure, to the adrenal hormones, cortisone, hydrocortisone or prednisone, and to adrenocorticotrophic hormone (ACTH), respectively

The term collagen stems from the Greek base *kolla*, which means glue or binding substance, thereby identifying the connective tissue of mesenchymal origin Collagen is the intercellular substance In juxtaposition are the fibroblasts with delicate fibrils as well as the elastic fibers, reticulum and *intercellular homogeneous ground* substance. The collagen and ground substance in the normal state are inconspicuous by the usual staining technics Significant alterations in the cellular structure and the ground substance occur in the

diffuse collagen diseases This change was identified as "fibrinoid degeneration" by Klinge [89] in 1933, a term first applied to pathologic findings by Neumann [123] in 1880. A proliferative reaction associated with an increase in the number of fibroblasts and an increase in intercellular substance occurs in some instances, in others, degenerative changes predominate. Hematoxylin and eosin stain produces a strong eosinophilic reaction when collagen becomes granular and the ground substance visible, while silver stain brings out strands of fibrin Infiltration with leukocytes completes the picture Thus, evidence of inflammation, proliferation and degeneration may be noted microscopically

Characteristic alterations in the connective tissue are illustrated best by the microscopic findings in pathologic material from patients with systemic lupus erythematosus The connective tissue of the blood vessels in polyarteritis and thrombotic thrombocytopenic purpura suffers the major insult that leads to the diffuse vascular changes The muscles and skin appear to bear the brunt of the pathologic damage in acute dermatomyositis and systemic scleroderma

The etiology of each of the several conditions to be reviewed is unknown Hypersensitivity is believed to be an important feature in the production of the vascular lesions of polyarteritis and thrombotic thrombocytopenic purpura. even though conclusive evidence is lacking Except for polyar-

Nor has it been possible, until recently, to induce experimentally in humans, any facsimile of these maladies The exception is the peculiar syndrome that has been recognized in patients who have received hydralazine for a period of time in the treatment of hypertension The syndrome which developed in a small number of patients appeared to be indistinguishable from SLE It is equally significant that the LE cell phenomenon has been demonstrated in the blood from some of these individuals Clinical findings regressed rapidly

following discontinuance of the hypertensive drug. follow-up period will be required in order to detern ultimate impact upon the body of this iatrogenic sy. Since SLE is characterized by long remissions in sing stances, regression of symptoms following cessation therapy does not mean necessarily complete restoratic tissues that have suffered injury.

In spite of the significant increase in the inciden several maladies and the increased recognition earlic clinical course, effective treatment has not been devis group of disease constitutes, therefore, a serious problem in treatment as well as in understanding etiology and pathogenesis of the morbid states

Systemic Lupus Erythematosus

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE), a malady of unknown etiology, with a predilection for females, is characterized by a cutaneous eruption on the malar prominences and over the bridge of the nose, resembling a "butterfly" in configuration (PLATE I, page 1) In the acute phases of the malady, as well as terminally, alarming constitutional symptoms from extensive visceral involvement are to be expected The disease may be chronic in duration, and the time of onset of symptoms frequently difficult to discern Furthermore, early seemingly unrelated symptoms may be accepted subsequently as initial links in the chain of clinical and pathologic events Most patients succumb ultimately to the disseminated disorder of connective tissue

The variability of the clinical course has led some observers to attempt to classify patients with this malady into an acute, subacute or a chronic type [*80*], a differentiation probably of little intrinsic value [*30*] More important is the frequency with which benign chronic discoid lupus manifests generalized changes sufficient to justify a diagnosis of disseminated lupus Although it is not the usual experience of sagacious internists, who are concerned with a general medical service, to obtain a past history of chronic discoid lupus in patients with SLE, the experience of dermatologists has been reputed to be quite different The localized benign skin lesions of discoid lupus may be present in some patients under the care of such a medical practitioner for one or two decades before dissemination is apparent and clinical mani-

following discontinuance of the hypertensive drug. A long follow-up period will be required in order to determine the ultimate impact upon the body of this iatrogenic syndrome. Since SLE is characterized by long remissions in singular instances, regression of symptoms following cessation of drug therapy does not mean necessarily complete restoration of the tissues that have suffered injury.

In spite of the significant increase in the incidence of the several maladies and the increased recognition earlier in the clinical course, effective treatment has not been devised. This group of disease constitutes, therefore, a serious medical problem in treatment as well as in understanding of the etiology and pathogenesis of the morbid states.

Systemic Lupus Erythematosus

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The variability of the clinical course has led some observers to attempt to classify patients with this malady into an acute, subacute or a chronic type [80], a differentiation probably of little intrinsic value [30] More important is the frequency with which benign chronic discoid lupus manifests generalized changes sufficient to justify a diagnosis of disseminated lupus Although it is not the usual experience of sagacious internists, who are concerned with a general medical service, to obtain a past history of chronic discoid lupus in patients with SLE, the experience of dermatologists has been reputed to be quite different The localized benign skin lesions of discoid lupus may be present in some patients under the care of such a medical practitioner for one or two decades before dissemination is apparent and clinical mani-

festations of SLE develop A similar observation has been made in selected instances of the progression of rheumatoid arthritis into SLE. A diagnosis of rheumatoid arthritis has been presumed initially in some patients and supported by satisfactory clinical evidence for months or even years, following which and without a recognized pathogenic mechanism, the clinical findings of SLE become apparent [*8*].

The conventional term acute disseminated lupus erythematosus has been criticized justifiably as an inappropriate appellation for the malady under discussion. "Acute" usually refers to the severity of the clinical symptoms, although it may refer to the severity of pathologic findings in some patients. "Disseminated" was introduced originally to describe widespread skin lesions of the chronic discoid type without reference to constitutional involvement. "Lupus" referring to a tuberculous etiology obviously is inept "Erythematosus" is a misnomer in patients failing to develop cutaneous manifestations. Harvey and associates [*59*], Haserick [*60*], Keil [*81*] and others prefer the term systemic lupus erythematosus While the traditional term, acute disseminated lupus erythematosus, enjoys the advantage of established usage and is more widely accepted, it will be replaced by systemic lupus erythematosus (SLE) in this discussion because of preference by those competent to pass judgment.

HISTORICAL

Biett is credited with describing the discoid form of lupus as "érythéma centrifuge" in 1828 [*14*]. Hebra [*67*] and Cazenave [*20*] in the following decades made significant contributions to the description of this malady. "Lupus érythémateaux (Erythéma centrifuge)" is the title of the communication by Cazenave which was published in 1851 Except for one statement, the clinical description of four patients suggests that they were suffering from the discoid type. Comment is made that *rheumatism* appeared in one of the patients, necessitating confinement to bed for several weeks Photosensitivity and predominance of females was noted also.

associates, Jarcho [73] reviewed the pathologic material from a group of cases with this dyscrasia at the Johns Hopkins University Hospital, and called attention to the "onion skin" lesions of collagen in the splenic arterioles Ginzler and Fox [48] in 1940 described hematoxylin staining bodies in the heart valves, lymph nodes, kidneys and spleen. Klemperer, Pollack, and Baehr [444] used the term *diffuse collagen disease* in its current sense in a communication published in 1942. The first case in Denmark was described in the same year [120]

In 1948, Hargraves and associates [57] made the latest and most important advance in the experimental confirmation of the clinical diagnosis of this malady. The discovery of the "LE cell" permitted, for the first time, confirmation of the diagnosis ante-mortem. The diagnostic significance of the LE cell, substantiated shortly after by Haserick and Bortz, [63] continues to enjoy high esteem. During the two decades prior to the observation by Hargraves, a number of investigators made important clinical or pathologic contributions in the field We have included in this group Banks [6], Christian [21], Friedberg and associates [45], Gross [54], the Reifensteins [135] and Tremaine [158]. Undoubtedly others would modify or supplement this list.

INCIDENCE

The apparent progressive increase in incidence of SLE is widely recognized and generally accepted. In 1892, Morris [118] confessed that "Kaposi's third variety (SLE) in which the constitutional symptoms are of intense severity and the disease often ends in death, I have never met with in my own practice, nor have I heard of cases in the practice of other dermatologists in England. I can only conjecture that in these cases the local affection becomes complicated by erysipelas or some other acute infectious process grafted on it." During the first three decades of our century there were only isolated case reports of patients with this morbid affliction In the 1930's, a significant increase in incidence began to attract

the attention of dermatologists and internists In 1933, Keil [*79*] collected 125 cases of lupus erythematosus from the literature in which the diagnosis was acceptable clinically In 1937, he reported the findings from 60 cases of the malady in which post-mortem examinations had been performed in 70 per cent [*81*] The following year, Ludy and Corson [*104*] stated that the literature had increased decidedly during the preceding decade and that the disease occupied a place second to syphilis in the number of contributions to dermatologic publications A tabulation by these observers of a group of records *prior to 1936 revealed that the incidence of lupus was* only 0 72 per cent of all cutaneous diseases The incidence had increased to 2 67 per cent in 1936 and had moved from the 24th place on the list of diagnoses to the 11th place Dubois [*32*] has reported the experience in recent years at the Los Angeles County General Hospital The diagnosis of acute lupus was made in 11 patients in 1949 During the following two years it was made in 44 patients Haserick [*62*] has summarized his experience since 1948 at the Cleveland Clinic One hundred and twenty six patients with positive LE cell tests were observed during a period of six years only Aegerter and Long [*1*] in 1949 estimated the incidence of SLE to be 50 per cent of that observed for acute rheumatic fever Twenty years ago a case of SLE was an oddity on the medical service in a large general hospital In recent years, it is not unusual for several cases to be on the service at one time with an incidence apparently greater than that of acute *rheumatic fever*

The onset of symptoms has been noted as early as the eleventh month of life or as late as the seventy-third year [*44*] The average or median age at onset corresponds to the distribution curve that shows a peak in the second, third and fourth decades of life The average age, however, was 48 5 years in the series reported by Leikola and Varta [*98*] In the older age groups, symptoms suggestive of rheumatoid arthritis frequently precede the clinical presumption of S [*142*].

Baehr, Klemperer and Schifrin [3] were among the firs to call attention to the preponderance of females affected. Th onset of symptoms usually occurs between the genesis o menses and their cessation From 80 to 90 per cent of th patients in most large series have been females The ex perience of the Armed Forces during World War II is sig nificant in this regard [4]. In spite of a heavy preponderanc of males over females in the military population, the rati was similar to that of the civilian series, i e, 4:1, in favor o the females Members of this sex with red hair or a light sensitive complexion are believed to be more susceptibl [17].

The racial incidence of SLE appears to be similar to th distribution of races in the general population Shearn an Pirofsky [149] noted the diverse racial background among their patients, which included Jews, Italians, Puerto Ricans and Irish as well as patients whose families were native to South America, Scandinavia, Central Europe or Eastern Europe The pigmented skin of the Negro does not protect against development of the malady. There are several instances of the familial occurrence of SLE [17, 149] Cases are reported also of SLE in families in which other members have chronic discoid lupus or rheumatoid arthritis [62, 74].

RELATION TO OTHER COLLAGEN DISORDERS

A diagnosis of rheumatoid arthritis, acute rheumatic fever or Raynaud's syndrome may be made in some patients before a suspicion of SLE is entertained A clinical diagnosis of SLE may be substantiated in other instances by appropriate laboratory studies Concomitantly, clinical symptoms suggestive of rheumatoid arthritis or acute rheumatic fever may be observed [105] Cohen and Cadmen [23] reported that six out of seven patients with SLE had symptoms of "rheumatism" at some time in the clinical course The diagnosis of "rheumatoid arthritis" was noted by name in three patients in their case abstracts, and "rheumatism" in the

others Friedberg and associates [*15*] reported joint deformities in two patients with SLE similar to those in rheumatoid arthritis Shearn and Pirofsky [*149*] detected findings upon physical examination in four out of 34 cases that were similar to those considered to be typical of rheumatoid arthritis Raynaud's phenomenon, subcutaneous nodules (rheumatic ?), and myositis have been observed initially or during the course of either malady [*32, 74*] Fever, malaise, loss of weight and other constitutional symptoms provide rather convincing clinical evidence in support of a diagnosis of rheumatoid arthritis [*143*] Roentgenographic changes in the joints may be indistinguishable Perivascular focal collections of lymphocytes and plasma cells in the connective tissues and in the sheaths of muscles and nerves were noted by Morrison and associates [*119*] in eight out of nine cases of SLE The microscopic findings were judged to be indistinguishable from those that might have been detected in rheumatoid arthritis

The clinical manifestations of acute rheumatic fever have been observed in some patients who show also inferential evidence of SLE Each of four patients reported by Libman and Sacks [*100*] revealed a sufficient number of clinical manifestations to suspect acute rheumatic fever A coincidental diagnosis of dermatomyositis was also made in one Bauer, Riley and Cohen [*9*] described the appearance of Sydenham's chorea in a 17-year old Negress Symptoms indicative of SLE developed six weeks later Typical lesions of SLE as well as those of rheumatic valvular heart disease were demonstrated at autopsy Pathologic features that may be useful in differentiating these maladies have been described by Gross [*51*] The absence of palisading and Aschoff bodies, the atypical location of the vegetations on the heart valves, and a marked tendency to necrosis of the valves are peculiar to SLE Massell and associates [*108*] reported the pathologic findings in a subcutaneous nodule that had been induced in a ten-year-old girl suffering from SLE The features helpful in differentiating the changes from a rheumatic nodule were

resented Symptoms of Raynaud's syndrome may develop SLE, scleroderma or acute dermatomyositis, early in the inical course or only after the respective entities have been resent for a sufficient length of time to warrant a diagnosis a generalized disturbance.

Banks [6] was one of the first to discuss at length the erns of similarity and dissimilarity in each of the unusual llagen disorders Overlapping of clinical findings as well as oss-matching of pathologic changes emphasizes the diffi- lties in precise identification [2]. Patients with apparent mptoms of SLE initially may show unmistakable evidence on post-mortem examination of one of the other afflictions clinicopathologic discussion by Soma Weiss [106] is illus- ative of the difficulty in differentiating the clinical findings SLE from the microscopic findings of polyarteritis. Clin- al examination of the patient under consideration left little ubt regarding the diagnosis of SLE The pathologic find- gs, on the other hand, were characteristic of polyarteritis, ot of SLE Another example is the case reported by Shaffer 46] The patient suffered from cutaneous lesions, fever and ukopenia. A skin biopsy was consistent with a diagnosis of .E Sulfonamides were prescribed in treatment. Character- tic lesions of erythema nodosum appeared several years ter The biopsy specimen then revealed the vascular anges of polyarteritis. Nor has the discovery of the LE cell enomenon eliminated confusion completely between SLE d polyarteritis Baggenstoss [5] observed a patient with in lesions that were believed to be characteristic of SLE e LE cell phenomenon was demonstrated upon examina- on of the bone marrow Post-mortem examination revealed idespread arterial lesions indistinguishable from those ob- rved in typical cases of polyarteritis It has been noted also at dermatomyositis [74], scleroderma [40, 49] and throm- otic thrombocytopenic purpura [510–511] possess several atures in common with SLE [30]. Evans [40] reported an nusual form of alopecia capitis in two patients with SLE d one patient each with scleroderma and dermatomyositis

A comprehensive discussion of the differentiation between dermatomyositis and lupus was presented by Keil [82] in 1940, to which the interested are referred Other instances of the overlapping of certain components among the unusual collagen diseases will be discussed in the chapters that follow

The potential relationship of chronic discoid lupus to SLE has generated considerable difference of opinion in the literature As noted in the Introduction, the dermatologists have been strong supporters of the belief that chronic discoid lupus and SLE have considerably more in common than similar names [113] In 1939, Belote [11] stated that, "The localized discoid form is generally recognized as of slow growth and commonly associated with a good prognosis as far as life is concerned Yet under certain influences it may disseminate as either the discoid or the exanthematous type " Wilson and Jordan [162], in a report from the Dermatology Service at the Buffalo General Hospital, discussed the transition from chronic discoid lupus to the acute disseminated form, particularly following exposure to the sun, ultraviolet radiation, x-ray therapy, interference with chronic infection, or with gold therapy. Approximately 20 per cent of a series of 96 patients with SLE collected from the literature had a past history of benign discoid lupus Twenty-six per cent of the cases classified as subacute lupus also had a history of the discoid type. Since some of these undoubtedly would progress into the acute disseminated form at a subsequent time, the probable final percentage datum is significant Among the dissenters are Baehr and Levitt [4], whose opinion commands respect "The authors also believe that it (SLE) is unrelated to that benign indolent skin lesion known to dermatologists as discoid lupus erythematosus, with which its more chronic form has sometimes been confused " The prevailing sentiment, however, seems to favor a relationship that is more than coincidental The development of systemic manifestations in patients who previously had complained only of discoid lesions has been reported following the administration of heavy metals, antibiotics, iodine and vaccines

—agents which are associated with the development of hypersensitivity Equally pertinent is the *reversion from systemic symptoms to discrete lesions* Haserick [*62*] recorded nine instances of reversion of the erythema in SLE to discoid lupus following therapy This phenomenon occurred spontaneously in one patient in a study reported by Cohen and Cadmen [*23*]

ETIOLOGY AND PATHOGENESIS

Inciting agents—physical, chemical, and bacteriologic —have been indicted *in the pathogenesis of SLE, but* acceptable evidence demonstrating cause and effect is lacking. The tuberculous etiology has been championed by French investigators but has never enjoyed general favor [*118*]. This explanation fell into disrepute as a result of the critical studies of Keil [*79*] and others The etiologic implications between a streptococcal infection and SLE cannot be abandoned so readily The inter-relationship between SLE, rheumatoid arthritis and acute rheumatic fever suggests that a streptococcal infection may be a contributing factor, even though convincing experimental data have been presented for acute rheumatic fever only. O'Leary [*125*] expressed the sentiment in 1934 that "The causation of the disease has not been explained, although evidence indicates that it is of underlying bacterial origin" In spite of the fact that clinical observations of the natural history of SLE suggest that a bacterial infection or a bacteremia may be the inciting phenomenon, blood cultures usually are sterile, except terminally Also, the pathologic findings do not confirm a presumptive bacteriologic etiology of the malady [*4*, *120*]. Serum antistreptolysin O and the streptococcal antihyaluronidase titers were investigated by Rantz and associates in six patients with SLE [*134*] The normal values observed in *each patient argued against a recent streptococcal infection.*

Hypersensitivity to bacterial products was proposed as the pathogenic mechanism by Stokes [*153*] in 1932. Rich [*137*] championed the hypersensitivity hypothesis some time

later in interpreting the pathologic findings in rheumatoid arthritis, acute rheumatic fever and periarteritis, as well as in SLE Mortensen and Gormsen [*120*] also have expressed the belief that systemic lupus is an allergic reaction to one of a variety of antigenic agents Contrary views are held by Baehr and Levitt [*4*] and Baggenstoss [*5*] A review of the case histories of patients suffering from SLE with instances of untoward sensitivity to drugs, vaccines, serum, transfusions of intercurrent infection [*17*, *56*] is impressive Convincing proof, however, is not yet forthcoming

There are two observations that lend support to the hypersensitivity theory of causation An anticomplementary serologic test for syphilis [*136*] is a relatively common phenomenon in patients with SLE It is curious that similar reactions have been noted in multiple myeloma The second item relates to the widespread use of sensitizing chemotherapeutic agents, particularly the antibiotics, during the past twenty years A significant increase in incidence of SLE two decades ago was believed to have been associated with the widespread use of sulfonamides after their introduction into medicine in the 1930's The incidence has continued to show a progressive increase during the past decade with the administration of stupendous quantities of penicillin and other antibiotics as they became available The development of the LE cell phenomenon in patients sensitive to penicillin has been advanced as additional evidence in support of a hypersensitivity theory of causation

Frequently multiple sensitivities are observed in SLE Some of the cases recognized as having penicillin reactions with LE cells, have been demonstrated subsequently to have SLE In view of the frequency of penicillin reactions, the appearances of the LE cell is unusual under these circumstances One might speculate that these particular penicillin reactions may be *effect* rather than *cause* Long periods of observation may be required for definitive clinical data Therefore, cautious interpretation of the basis for appearance of the LE cell phenomenon is indicated This would seem to

apply not only to the LE cell in penicillin reactions, but also to other drug reactions and complicating clinical states. So far, the LE cell phenomenon has seemed to be a unifying force in diagnosis

A related phenomenon is the recognition recently of an iatrogenic syndrome similar to SLE. It is hoped that this observation may furnish an important clue to the pathogenesis of connective tissue disorders. Dustin and associates [*36*] at the Cleveland Clinic reported an SLE-like syndrome following prolonged therapy with large doses of hydralazine in the treatment of hypertension. Fever and arthralgia appeared as the initial untoward reactions Symptoms suggestive of rheumatoid arthritis and of SLE were observed later. The identification of LE cells in the blood, a false-positive serologic reaction, and an elevated globulin appeared to substantiate the clinical evidence. A complete or an incomplete syndrome was observed in 13 out of 119 patients treated with hydralazine. Perry and Schroeder [*129*] recorded the development of SLE-like symptoms in 17 out of 210 patients treated with a combination of hexamethonium chloride and hydralazine Shackman and associates [*145*] observed the appearance of the syndrome in a 59-year-old female after a total of 65 Gm of hydralazine had been administered over a period of nine months Stunkard, Wertheimer and Redish [*154*] have suggested that hydralazine acts upon the blood vessel wall in producing SLE-like findings Complete regression of signs and symptoms of SLE and regression of abnormalities in the laboratory tests may be expected within a few weeks after discontinuance of the inciting drug. Except for the production in animals of vascular lesions similar to those seen in polyarteritis, the development in humans of an SLE-like syndrome following hydralazine is the only evidence available of the experimental production of any of the collagen disorders.

Photosensitivity has been recognized for some time as a precipitating factor in the production of local and systemic manifestations, although it may not be intimately related to

the pathogenesis of SLE Baehr and associates [3] observed that exposure to the sun immediately preceded the onset of symptoms in some patients, in others, already afflicted, a sunburn was followed by a severe recurrence of the illness, and the characteristic features of the disease became more evident Jessar, Lamont-Havers and Ragan [74] reported a 27 per cent incidence of sensitivity to the sun, and Montgomery [115] a 23 per cent incidence of sensitivity in SLE patients Exposure to the sun followed by a severe reaction preceded the onset of symptoms of SLE in six of Jessar's patients Tumulty and Harvey [160] reported photosensitivity in most of the cases reviewed by them One patient had a typical butterfly lesion which followed exposure to the sun each summer for twelve years prior to the onset of constitutional symptoms Baehr and associates [3] observed that none of their patients had had a history of photosensitivity prior to the onset of the disease A search of the blood and urine for porphyrins was made in two cases with negative results Yet the possible association with porphyrin metabolism deserves further investigation There are isolated instances of an exacerbation of symptoms following exposure to cold [7, 82, 147] Gahan [46] investigated the incidence of SLE as a function of climatic conditions A review of statistics from the United States, South America, Europe, Australia, Japan, India and the Philippine Islands demonstrated no significant correlation between climate and the incidence of the malady

The high incidence of the disease between puberty and the menopause in females has suggested an endocrine pathogenesis No instances, however, were discovered in the literature reviewed of an intimate association between the development of symptoms and the onset of puberty Pregnancy, on the other hand, has commanded considerable attention in this malady Ellis [38] reviewed the prenatal course of 56 patients with SLE and ascertained a worsening of the disease in 45 per cent The maternal death rate was 25 per cent, and the fetal death rate nearly 30 per cent Contrariwise, 11 per cent

showed some improvement during pregnancy No effect upon the mother or the pregnancy was noted in patients with chronic discoid lupus in this study Interruption of gestation has been recommended because of the progression of the disease during pregnancy Therapeutic abortion probably is not warranted, however, since this procedure has not been attended with demonstrable benefit [29] Natural menopause has been observed to have no consistent effect upon the clinical course of SLE [38], and therapeutic castration of women has not been followed by alleviation of systemic symptoms [115] Also, treatment with large doses of testosterone, in order to counteract estrogenic activity, has been followed by essentially negative results It may be concluded that endocrine functions peculiar to females bear no recognized relation to the manifestations of SLE [4].

Coburn and Moore [22] postulated that altered cellular metabolism, associated with an increased concentration of serum gamma globulin, was responsible for the pathologic process Ehrich [37] has carried this possibility a step further He has implicated the plasma cells in the production of gamma globulin and has included each of the collagen disorders in this theory of pathogenesis. The abnormal globulin is presumed to react upon mesenchymal tissue with release of mucopolysaccharides, fibrinogen and other substances from damaged tissue *Reference may be made at this point* to the likely possibility of an abnormal globulin in the formation of LE cells. This subject will be discussed later.

PATHOLOGY

Gross changes at post-mortem examination may be meager except for cutaneous involvement. They are disproportionately slight when correlated with the extent and severity of clinical symptoms [22] "Although SLE has been characterized classically as a malady with diffuse exudative manifestations, gross effusions into the pericardial sac, the pleural cavities, the abdominal and synovial spaces, respec-

tively, are unusual Nonbacterial endocardial lesions may be noted on the heart valves and on the mural endocardium Enlargement of the liver and spleen and diffuse lymphadenopathy may be apparent Except for the sterile verrucal vegetations and cutaneous manifestations, there may be little upon gross examination to suggest the correct underlying pathologic process

The lesions observed microscopically may be equally deceptive Mallory, in his clinicopathologic sessions at the Massachusetts General Hospital, more than a decade ago, described the microscopic findings in SLE as nonspecific, and held the opinion that the malady frequently was a challenge to the pathologist because of the absence of identifying features [*105, 107*]. In such instances, the microscopist must rely heavily upon the clinical and laboratory data in order to help resolve an unknown [*5*] This discouraging sentiment probably does not prevail at present, since significant identifying features are being reported regularly These include the proliferative, degenerative and inflammatory changes in the connective tissue, quasi-specific vascular lesions, the hematoxylin-staining bodies, the "wire loop" lesion in the kidney, the perivascular fibrosis in the spleen, and the changes in the skin, respectively No one of these lesions is peculiar to lupus, but the identification of one or more microscopically is helpful in supporting a diagnosis of SLE

Connective Tissue

Since the microscopic changes in collagen have been described meticulously and have been identified so intimately with the investigations of Klemperer, Baehr and associates [*3, 88*], excerpts from their communications will be used freely The term *fibrinoid degeneration* has been applied "to the altered ground substance giving the same tinctorial reactions as the altered fibers The alteration of fibers and ground substance is accompanied by a conspicuous proliferation of fibroblasts Less conspicuous is the infiltration of histiocytes

and leukocytes The fibroblasts are concentrated in the foci of altered collagen fibers. The cytoplasm is often basophilic and attenuated, even fibrillar in appearance. The nuclei are pyknotic or fragmented. There is sometimes chromatolysis with suffusion of the basophilic nuclear material into the cytoplasm and intercellular ground substance.

"The thick, gelatinous, adherent pericardium owes its arresting gross appearance not only to proliferative and infiltrative tissue changes but even more to a series of alterations affecting the pre-existing and the newly-formed connective tissue. . . In hematoxylin-eosin preparations the fibers, cell cytoplasm, and ground substance can be optically isolated under high magnification only by 'stopping down' the diaphragm of the substage condenser. In the Mallory trichrome stain the ground substance assumes a pale blue homogenous appearance, in which the deeper blue collagen fibers stand out quite clearly The ground substance may be thought to have become 'collagenized '

"Not only does the ground substance become visible, but it also increases in bulk, as evidenced by splitting off of individual fibrils from large collagen bundles and wide separation of these fibrils and connective tissue cells.

"Finally, fibrinoid degeneration affecting both fibers and 'collagenized' ground substance is often quite conspicuous in the grossly thick, gelatinous-appearing, adherent pericardium."

Vascular Lesions

The changes in the vessels of the kidney, lung and spleen will be discussed separately. There may be considerable variation in intensity and extent of vascular damage to the systemic vessels, but most organs and tissues of the body may be involved Quoting again from Klemperer and associates [88]: "In the most severe lesions there was complete necrosis of arteries and particularly of arterioles . . . The mildest recognizable change is a deposit of homogeneous, eosino-

philic material (so-called fibrinoid) within the intima, between muscle fibers of the media or within the adventitia. It is generally accompanied by fibroblast proliferation In the intima this proliferation often results in considerable narrowing of the lumen without any participation of the endothelium The newly-formed fibroblasts generally exhibit degenerative changes as evidenced by distortion of the nuclei and by pyknosis

"Further progression of this process leads to involvement of more and more of the vessel wall so that in the intima complete rings of fibrinoid masses are laid down, lifting the endothelium from the media and choking the lumen . With complete fibrinoid change of the collagenous framework of the vessel wall, destruction of muscular and elastic elements ensues In this phase there is a striking proliferation of adventitial cellular elements, which show degenerative changes While in most cases the definitive necrosis of the vessel wall can be recognized as the most advanced phase of the series of fibrinoid changes just elaborated, we have, on the other hand, observed fulminating necrosis of the entire vessel wall not associated with fibrinoid

"In three cases, fibrinoid changes of the connective tissue of the wall of small and medium-sized arteries—up to the size of large interlobular arteries of the kidney—was associated with massive necrosis of the muscular and elastic lamina of the walls. In these cases there was a striking inflammatory cellular reaction surrounding the necrotic foci and extending into the adventitia Lymphocytes, plasma cells and a few polymorphonuclear leukocytes were found together with the proliferating adventitial cells All of these cellular elements exhibited degenerative nuclear changes The severity of the injury of the vessel wall was evidenced by the formation of small aneurysms, but no perivascular hemorrhage was seen It is noteworthy that thrombosis is not found in the wake of even such damage In the later stages the necrotic tissue is replaced by a cellular connective tissue It is obvious that such lesions bear a striking resemblance to the

necrotizing arteritis of Meyer's and Kussmaul's periarteritis nodosa."

Skin

The early microscopic lesions in the skin comprise severe atrophy of the epidermis, dilatation of the capillaries and lymphatics of the superficial layers, and edema in the deeper layers of the rete [*341*]. Other abnormalities include hyperkeratosis, keratotic plugging of the hair follicles and sweat ducts, preservation of the granular layer, thickening of the prickle cell layer with adjacent regions of atrophy, liquification necrosis of the basal cell layer, and a perivascular, chiefly lymphocytic, infiltration about the dermal appendix [*39, 113, 114*]. Many of these alterations have been observed also in chronic discoid lupus. The description of the cutaneous lesions by Klemperer and associates [*88*] concentrated upon the fibrinoid degeneration of the ground substance and fibers as "evidenced by eosinophilic clumping of the former and by irregular thickening and straightening of the latter together with the acquisition of increased acidophilia and refractility. In the most advanced lesion the clumped fibrinoid masses break up, and some of the fragments become basophilic. Similarly, some of the swollen fibers acquire an affinity for hematoxylin and also become fragmented . . . Concomitant with the changes of fibers and ground substance there is proliferation of fibroblasts to a variable degree. These cells almost uniformly exhibit degenerative phenomena—distortion, pyknosis, necrosis. . . . The fibroblasts, however, exhibit both proliferation and degenerative stigmas, which seem to indicate involvement of the connective tissue . . . Even in the more severe cutaneous lesions the capillary endothelium may remain intact in the presence of fibrinoid degeneration of its collagen wall (basement membrane) and adjacent connective tissue . . . Lesions of the larger vessels—arterioles and smaller arteries—follow the same pattern already detailed in the description of the vascular changes in other organs. Here again the vascu-

lar lesion is evidently determined by involvement of the connective tissue matrix of the corium which is continuous with the connective tissue of the vessel wall "

Montgomery and McCreight [115] were unable to confirm the collagenous changes with fibrinoid degeneration upon examination of the skin of patients in their clinic In a survey of 96 biopsy specimens, alteration of the collagen and fibrinoid degeneration was observed in less than 25 per cent of the total Jessar and associates [74] reported observations upon 16 patients in whom the diagnosis was confirmed at autopsy The pathologic changes were characteristic in only three of the nine who had had a skin biopsy It is concluded that microscopic study of skin obtained at biopsy may be helpful in diagnosis, but is not specific

Kidneys

The kidneys appear larger than normal upon gross examination and the surface smooth with petechial hemorrhages The significant finding microscopically is the alteration in the glomerulus [152] The "wire loop" artifact described by Baehr, Klemperer and Schifrin [3] is produced by hyaline thickening of the basement membrane of the glomerular capillaries which stains intensely with eosin (PLATE II, page 1) This feature was recognized in 13 out of 23 cases in their original series Endothelial proliferation may be minimal or so disseminated as to lead to occlusion of the glomerular capillaries Focal necrosis of the glomerular tufts and hyaline thrombi may be identified also The similarity to embolic glomerulonephritis, a complication of subacute bacterial endocarditis, has been noted The "wire loop" changes have been observed also in isolated instances of eclampsia, scleroderma and malignant nephrosclerosis [5] The lesion is considered to be quite unlike the hyaline degeneration usually seen in chronic glomerulonephritis

It is believed that the apparent inconsistencies and the significance of "wire loops" in SLE have been adequately resolved by Klemperer [86] An examination of an un-

selected group of 43 cases of subacute or chronic glomerulonephritis disclosed a "wire loop" change in five instances. The extensive changes of glomerulonephritis were apparent in the glomerular tufts as well as throughout the tubular apparatus. On the other hand, in the kidneys from patients suffering from SLE, microscopic changes of glomerulonephritis were encountered in only two out of twenty that showed the characteristic lesion. The "wire loops" in glomerulonephritis are believed to represent but one component of the inflammatory triad. The "wire loops" of SLE, on the other hand, are not associated usually with exudation and proliferation and represent "a primary and fundamental collagen degeneration which is similarly expressed in other organs. This cannot be demonstrated in glomerulonephritis." Tubular atrophy with focal interstitial collection of lymphocytes, plasma cells and histiocytes is not apparent except in cases with a long history and advanced glomerular damage. Hydropic vacuolization and fatty and hyaline droplet degeneration in the proximal convoluted tubules may be noted. Alteration in the renal arterioles may mimic the changes of malignant nephrosclerosis or polyarteritis [5].

Heart

The description by Libman and Sacks [*100*] of a nonbacterial endocarditis embodies one of the two characteristic pathologic findings in the heart of patients with SLE. The incidence of endocarditis in SLE has been reported to be as high as 60 per cent. The vegetations range in size from 1 to 4 mm. in diameter and may become infected with common bacterial pathogens in the terminal phase of the malady [*4*]. They occur singly or in small conglomerates as mulberry-like excrescences near the edge of the valves, on the chordae tendinae, and on the papillary muscles. They develop away from the line of closure of the valve and appear on either side of the leaflet without preference. Mural endocardial lesions occur near the base of the ventricle rather than proximal to the apex of the heart [5]. The endocardial lesion on the

valves, upon histologic examination, appears to be only the surface manifestation of an intense valvulitis Extensive fibrinoid degeneration of collagen protrudes onto the surface of the leaflet, becomes grossly visible as a vegetation, and is accompanied by necrosis of cells and fibers The exudative reaction is more intense than that which usually accompanies rheumatic valvulitis The necrosis leads to the development of granular basophilic masses which encompass nuclear debris, basophilic fragments, cytoplasm and fibrils These are the components of the hematoxylin-staining bodies described first by Gross [54]

Hematoxylin-staining bodies, the second identifying lesion in the heart in SLE, have acquired meaningful diagnostic value in recent years The chromophilic bodies have been observed in mesenchymal tissue, lymph nodes, kidney, lung and spleen, as well as on the heart valves The staining characteristics, believed to be related to the inclusion material in the LE cell, are conditioned by an alteration in the nuclei of cells of mesenchymal origin such as polymorphonuclear leukocytes, lymphocytes and fibroblasts Histochemical studies suggest that the hematoxylin-staining substance is derived from nuclear chromatin and represents depolymerized desoxyribose nucleic acid Klemperer and associates [87] reviewed the pathologic material in 35 cases of SLE in pursuit of the significance of the distinctive lesions They were identified in all except three of the cases Gueft [55] confirmed the high incidence of these lesions in SLE and failed to identify them in a control series of cases which included rheumatic and bacterial endocarditis, diffuse and focal glomerulonephritis, malignant nephrosclerosis and polyarteritis An exception is the observation of Worken and Pearson [163] Hematoxylin bodies were observed in the blood vessels from a patient who lacked the clinical findings of SLE and was thought to be afflicted with a variant of polyarteritis classified as fulminating granulomatous angiitis (Zeek)

Examination of the myocardium may reveal fibrinoid degeneration with exudation These changes present a sharp

contrast to the Aschoff bodies that are present usually in the heart muscle in acute rheumatic fever [3, 4] In the latter malady, fibrinoid degeneration is absent or minimal, and proliferative changes overshadow the exudative reaction [5] The incidence of fibrinous pericarditis in SLE is significant [160]. The exudate contains polymorphonuclear cells and fibroblastic organization (PLATE III, page 2) which obliterates the pericardial sac if healing is permitted

Lungs

There are several observations which indicate that specific microscopic alterations may be found in the lungs of patients with SLE. Rakow and Taylor [133] and later Foldes [43] described a chronic interstitial pneumonitis associated with atelectasis Baggenstoss [5] extended these observations and pointed out that one might observe also alveolar hemorrhage and a basophilic mucinous edema of the alveolar wall and of the peribronchial and perivascular tissues. The microscopic features could be differentiated from those usually seen in pyogenic pneumonia, either with or without organization. Seven of the 20 cases of Harvey and associates [59] that were suspected of having "lupus pneumonitis" were investigated post-mortem Involvement of the hyaline membrane in the alveoli, focal necrosis of the alveolar walls and capillary thrombi were identified The findings were similar to those observed in rheumatic pneumonitis, polyarteritis, anaphylactic pneumonitis due to sulfonamide hypersensitivity, or in serum sickness Teilum [155] has described a miliary *epithelioid-cell granuloma in the pleura and parenchyma* of one patient with SLE The microscopic changes were attributed to a "focal allergic pneumonia." Fibrinoid degeneration and focal necrosis were apparent in some areas, in others, fibrosis had developed The similarity to microscopic alterations in Boeck's sarcoid and primary amyloidosis was appreciated

Spleen

Examination of the spleen may disclose a lesion that is presumed by some to be pathognomonic of SLE, i e, periar-

terial fibrosis of the central arteries (FIG 1) The original description has been attributed to Libman and Sacks in their epochal communication of 1924 [*100*] Shaumann and Introzzi [*148*], a few years later, described the lesions in the spleen from three cases of lupus and considered the malady to be closely related to a dysfunction of the blood-forming organs Ginzler and Fox [*48*] rediscovered the lesions in the spleen in 1940 The fibrosis of the arterial wall assumes a pattern of concentric rings of thick collagen fibers with interstitial fibroblasts This feature represents collagenization of the normal fine reticulum The rings of collagen are laid down at the expense of the periarterial lymphatic tissue [*5*] The specificity of periarterial fibrosis of the spleen is noteworthy Kaiser [*77*] in his review of the pathologic findings in 18 cases of SLE, found these changes in 15 Contrariwise, the incidence of periarterial fibrosis was only 3 2 per cent in 1679 control cases. Klemperer [*88*] reported positive findings in 19 out of 20 cases of SLE Other observers have considered the lesions less specific [*156*], since they have been detected in patients who have suffered from acute rheumatic fever or from idiopathic thrombocytopenic purpura [*77*]

Involvement of Other Systems

In the examination of sections of muscle and peripheral nerves in 15 cases post-mortem, Lowman [*103*] observed a vascular pattern of reaction on the venous side of the circulation This included edema of the stroma, fibroblastic proliferation and fibrosis The changes were similar to those seen in patients with acute rheumatoid arthritis The synovial reaction in five cases was similar to the reaction seen in muscles and nerves Fibrinoid degeneration was observed in one specimen of muscle only Bennett and Dallenbach [*13*] reported microscopic changes in the synovial membranes of two patients with SLE who had not received steroids Articular symptoms had been present for several months before biopsy was performed The signs of inflammation comprised deposits of fibrin and fibrinoid changes in the synovial and

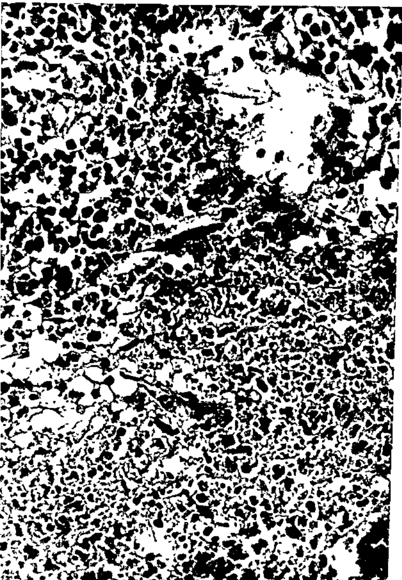


FIG 2—Photomicrograph of a lymph node from a patient who had died from SLE Extensive necrosis is illustrated

has been considered to be responsible for this depolymerization effect The LE cell appears to be a manifestation of this process, like the other tissue alterations The rather subtle nature of the pathology of SLE has undoubtedly delayed understanding of the process We are familiar with more dramatic findings in pathology

CLINICAL FINDINGS

The clinical characteristics of SLE are extremely varied Suspicion regarding the diagnosis may be delayed for weeks, months, or even years because of the great variation in clinical manifestations and in the incipient development of symptoms Malaise, joint distress and skin lesions, either together or independently, may be the initial complaint It would be rather far-fetched to suspect SLE on the basis of such vague evidence Symptoms frequently develop insidiously and with insufficient severity to cause the afflicted to seek medical attention Symptoms disappear spontaneously only to return at a later time in increased severity and in disturbing proportions Thus, it is possible for the disease to be present for a period of time without suspicion of the seriousness of the underlying process It is believed that, because of the fuller appreciation of the incidence, the malady will be suspected more often in the future, and the diagnostic criteria put to test in a greater number of those who are afflicted The variegated picture presented early in the course of the dyscrasia has been called the "LE diathesis" by Haserick [62] This includes hypersensitivity to infections and drugs, photosensitivity, frequent episodes of pneumonia, psychiatric stress or idiopathic epilepsy Acute pharyngitis, a tuberculin test, extraction of a tooth, or routine immunologic testing—each has been held responsible for the precipitation of acute generalized symptoms

A tabulation by Harvey [59] of the presenting complaints in SLE reveals a comprehensive list of symptoms Malaise, weight loss, fever, cutaneous lesions, arthralgia, lymphadenopathy, visual disturbances, pleurisy, precordial

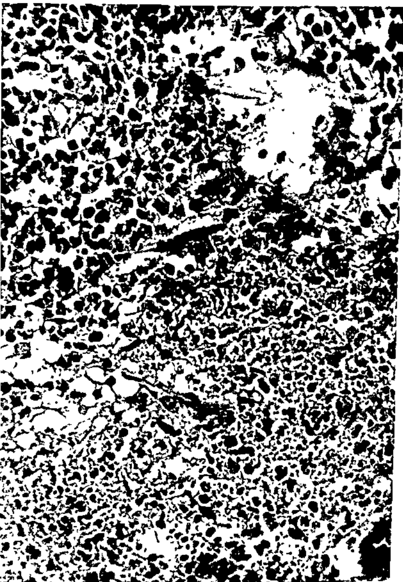


FIG 2—Photomicrograph of a lymph node from a patient who had died from SLE Extensive necrosis is illustrated

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distress, as well as symptoms referable to the gastrointestinal tract, genitourinary tract and central nervous system, respectively, have been noted. It is obvious that the triad of syphilis, tuberculosis and cancer, a favorite "pearl" in the differential diagnosis of a bizarre malady a generation ago, must be revised now to include SLE.

Fever was present at the onset in 25 per cent of the patients reported by Jessar and associates [*74*], and, at some time during the natural course of the disease, in 99 per cent of a total of 216 cases collected from the literature The temperature may show a slight elevation only and be remittent so as to suggest undulant fever, or it may be septic in type [*15*] Coburn and Moore [*22*] noted the absence of leukocytosis in their series of patients with fever. Malaise was present at the onset of the disease in 18 per cent of the cases reported by Dubois [*32*] and, together with weight loss, was noted in all patients some time during the course of the malady

The following is a composite list of presumptive diagnoses compiled by Harvey and associates [*59*] and by Haserick [*62*] in patients who were later proven to have SLE.

Acute nephritis
Acute psychosis
Acute rheumatic fever
Anemia
Brucellosis
Cerebral vascular accident
Dermatitis medicamentosa
Lymphoma
Meningitis
Nephrosis
Peripheral neuritis
Pleurisy
Pneumonia
Polyarteritis
Purpura
Dermatomyositis
Drug reaction
Epilepsy
Erythema multiforme
Felty's syndrome
Fever of unknown origin
Functional illness
Raynaud's syndrome
Rheumatoid arthritis
Septicemia
Scleroderma
Subacute bacterial endocarditis
Syphilis
Trichinosis
Tuberculosis

Skin

Because the descriptive term lupus erythematosus, i e, red wolf, identifies this malady, it might be presumed that

the cutaneous manifestations would be recognized in a majority of those afflicted In the memorable communication of Baehr, Klemperer and Schifrin [3], 22 out of 23 patients had a "butterfly" rash on the face However, a typical "butterfly" rash [67] has been reported in less than 50 per cent of the patients in most large series since then The incidence was only 27 per cent in Haserick's series [62] There is satisfactory clinical evidence that some patients may go through the entire course of the disease and at autopsy show unequivocal evidence of SLE, yet at no time have discernible skin lesions, i e, *lupus erythematosus disseminatus sine lupo* The patches of erythema which are distributed over the malar prominences and meet over the bridge of the nose may also appear on the lobe of the ear, the anterior triangle of the neck, the back, the chest, the shoulder, the arm, the hand, the terminal phalanges and the foot The distribution usually is symmetric, and gross atrophy of the cutaneous lesions is uncommon

Dubois [32] believes that the second most characteristic cutaneous lesion is the intense erythema which appears about the nailbed This lesion may progress to a purplish hue and be followed by ulceration and scarring. Petechial hemorrhages and telangiectasia may appear in the midst of the erythema Other skin manifestations include mucocutaneous ulcerations, silvering of the vermillion border of the lips, superficial whitish plaques of the buccal mucosa indistinguishable from the lesions of lichen planus [160], giant hives, erythema nodosum and purpura Subcutaneous nodules in SLE have been described by Hebra [67] and Kaposi [78] They may be as large as 2 cm in diameter and develop on the extensor tendons of the hands and wrists and other areas of the body Microscopically these lesions may resemble sarcoid or erythema induratum [112]

Joints and Muscles

Symptoms referable to the muscles and joints occupy a position that is second in clinical significance to the cutaneous manifestations Just as the care of patients with SLE in pr

vious generations frequently fell to the dermatologist bec
of cutaneous manifestations, in this generation, SLE, as
as the other unusual collagen disorders, come within
jurisdiction of the rheumatologist because of involveme
joints and muscles. Kaposi [78] was one of the first physic
to direct attention to the development of joint symp
which frequently preceded evidence of internal involven
Extensive and severe joint symptoms may be present f
decade or more before clinical evidence in support of a c
nosis of SLE is forthcoming [121]. The incidence of artl
gia may be as high as 90 per cent, while the incidenc
chronic joint changes with varying degrees of deformity
been reported to be as high as 30 per cent [82, 135]. S
patients show little objective evidence of articular invc
ment in spite of severe subjective complaints

The joints involved may be the same as those affecte
acute rheumatic fever or rheumatoid arthritis, i.e., ha
wrists, elbows, shoulders, ankles, knees, spine and hips
cardinal signs of inflammation may be observed in affli
joints. Articular symptoms appear, disappear and reapp
as in acute rheumatic fever Swelling, stiffness and resid
pain may be noted as in rheumatoid arthritis Involvemen
the proximal phalangeal joints of the hands, atrophy of
interossei muscles, and atrophy of the muscles of the the
and hypothenar eminences may be observed. Ulnar deviat
customarily seen in moderately advanced rheumatoid
thritis is unusual in SLE, as judged by the experience of K
[82] Ross and Wells [143] found the joint changes in
tinguishable from those of rheumatoid arthritis in more tl
one-fourth of their patients with SLE. The migratory nat
of the arthritis, resembling that in rheumatoid arthritis,
been emphasized by Baehr [4] and Slocumb [150]. Shea
and Pirofsky [149] have stressed the similarity of articu
symptoms in SLE to those in acute rheumatic fever Ho
ever, joint symptoms did not respond to salicylates as in ac
rheumatic fever, and sometimes showed little improvem
with the adrenal steroids These features were considered

be helpful in differentiating SLE from rheumatic polyarthritis

Heart and Blood Vessels

Clinical evidence of involvement of the cardiovascular system is discernible in more than 50 per cent of the patients suffering from SLE, with the pericardium, myocardium and endocardium possible sites of affliction A variety of cardiovascular symptoms and findings may be apparent upon clinical examination Libman and Sacks [100] were the first to call particular attention to changes in the heart in SLE Sterile verrucous endocarditis was found post-mortem in two patients with cutaneous manifestations of SLE Later Libman stressed the association of fibrinous pericarditis, white-centered petechia in the skin and constitutional symptoms This combination might suggest acute rheumatic fever or subacute bacterial endocarditis upon casual review However, he noted that fibrinous pericarditis is unusual in subacute bacterial endocarditis, and white-centered petechiae are not found in patients with acute rheumatic fever

Murmurs, usually systolic in time, are the most common findings that point to cardiac involvement A diastolic or a presystolic murmur, presumably indicates a Libman-Sacks type of endocarditis Griffith and Vural [53] observed no reliable correlation between the clinical findings on auscultation and the pathologic findings in the heart An apical systolic murmur was detected in seven patients with SLE, but only two of these revealed vegetations on the mitral valve In contrast, there were four additional instances of endocarditis The difficulty in interpreting the significance of a systolic murmur at the apex in the presence of anemia, fever and debilitation has been emphasized by Baehr and associates [3] Dyspnea, orthopnea, cardiac hypertrophy and failure may be the result of affliction of the heart muscle or of the coronary vessels, the latter an unusual complication [160] Gallop rhythm and hypertension are detected in a minority of instances Cardiac arrhythmias are uncommon

Premature beats, auricular fibrillation and first degree heart block [59] have been described.

Fibrinous pericarditis may be suspected from the clinical history or discovered upon physical examination in approximately 50 per cent of patients. The incidence at post-mortem examination is considerably higher. Persistent substernal distress or the detection of a precordial friction rub on auscultation is highly suggestive of fibrinous pericarditis. In selected cases, post-mortem examination has revealed extensive changes in the pericardial sac with neither symptoms nor physical findings to suggest involvement In some patients a large pericardial effusion has been reported. Dubois [32] observed one patient with acute pericarditis which cleared spontaneously four years before the diagnosis of SLE was confirmed by demonstration of the LE cell phenomenon Mortensen and Gormsen discovered no instance of constrictive pericarditis [116] upon extensive review of the literature Presumably, patients succumb to the malady before this complication is given an opportunity to develop. Electrocardiographic and post-mortem findings in eight patients with lupus were reviewed by Liebow and Feil [101]. The electric potential abnormalities consisted of low voltage, increased P-R interval, prolongation of Q-T interval, increase in left axis deviation, change of axis from normal to right axis deviation, and low or inverted T waves Serial electrocardiograms showed progressive changes with persistence of disease Various diagnostic procedures, which include radiographic, fluoroscopic and electrocardiographic examination of the heart, are to be recommended in the study of each patient with SLE.

Lungs

Pulmonary symptoms oftentimes are present in patients with SLE; sometimes they appear rather early in the clinical course This is not surprising in view of the incidence of involvement of the respiratory passages. Israel [71] discovered roentgenologic or pathologic evidence of pleuropulmonary

involvement in 90 per cent of 22 patients Pleurisy or a pleural effusion may be present intermittently for one or more years before evidence of other manifestations of the disease appears [32] Pleurisy in conjunction with pericarditis contributes to one of the classic syndromes of SLE, i e.,

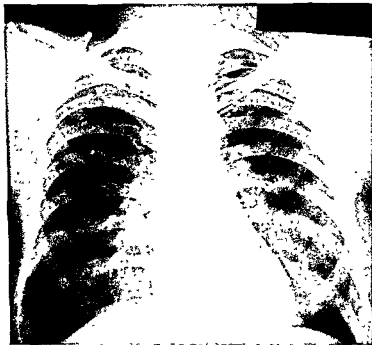


FIG 3—Roentgenogram of the chest of a patient who suffered from what was considered to be rheumatoid arthritis There is an increase in the peribronchial markings (see FIGS 4 and 5)

polyserositis Although cardiac and renal factors sometimes are responsible for accumulation of fluid in the pleural cavities, this manifestation usually is attributed to intrinsic changes intimately related to the connective tissue disorder.

Harvey and associates [59] have emphasized the parenchymal changes in the lungs, in contrast to the pleural involvement, which is more generally recognized A hacking

cough, sometimes dry, sometimes productive, and a few fine or coarse rales, may be the only signs pointing to parenchymal involvement Neither physical findings nor x-ray examination may reflect the magnitude of the affliction. A his-



FIG 4—Roentgenogram of the chest of the same patient as in FIG 3 This was taken 20 months later, at which time a clinical diagnosis of SLE was made There is an acute inflammatory process with an increase in the hilar masses and interstitial infiltration

tory of a "virus pneumonia" may be discovered before other manifestations of SLE appear A persistent interstitial pneumonitis [15, 133], considered to be typical of SLE, may lead to atelectasis and alveolar hemorrhage [5, 43]. Israel [71] has advised a search for LE cells in patients with recurrent pneumonia, a failure to respond to antibiotics, unexplained atelectasis, or pleurisy of unknown etiology.

The usual pathogenic invaders of the lungs which produce either acute or chronic involvement are observed frequently in the terminal state Pulmonary tuberculosis (FIGS. 3, 4, 5), pneumococcus lobar pneumonia and lung abscesses



FIG 5—Roentgenogram of the chest of the same patient as in FIGS 3 and 4 This examination was made two months following that illustrated in FIG 4 There is a marked increase in the infiltrative process Post-mortem examination showed miliary tuberculosis as well as disseminated lesions of SLE

have been noted in the closing phases of the disease The incidence of miliary tuberculosis in patients with SLE following adrenal steroid therapy has been noted by Walker [*161*] and Terplan [*157*] Before beginning steroid therapy, particular attention should be given to the search for tubercle bacilli in the sputum and gastric contents of patients

with pulmonary symptoms or x-ray evidence of parenchymal involvement. A calculated risk may be justified even in the presence of tubercle bacilli in the excreta, as will be noted under TREATMENT, page 68.

Gastrointestinal Tract

Nausea, vomiting, anorexia, abdominal pain, cramps, hematemesis and melena may be noted in patients with involvement of the gastrointestinal tract. The abdominal distress may be low-grade and not particularly disturbing or so severe as to suggest an acute surgical emergency. Vascular involvement of the wall of the bowel or other viscera is the usual explanation of these complications. Abdominal ascites sometimes is present. The prevalence of abdominal symptoms in SLE was noted by Osler [126]. The highest incidence in recent communications is given by Dubois [32], who reported that 40 per cent of the patients in his series suffered from abdominal complaints. Dysphagia and epigastric burning may reflect an extensive diphtheritic esophagitis associated with collagen degeneration and arteritis The small bowel was affected in three patients and the large bowel in five patients in the studies of Harvey and associates [59] Arteritis with ulceration of the mucosa was demonstrated at post-mortem examination. Peritonitis was present in seven out of eight cases examined post-mortem by Mortensen and Gormsen [120]

Liver, Pancreas, Spleen and Lymph Nodes

Some of the abdominal symptoms noted in the preceding paragraph may be attributed to the disseminated process in the liver, spleen, pancreas or lymph nodes The liver may be tender to palpation. Jaundice is an unusual complication Hepatomegaly may be demonstrable clinically with minimal evidence of liver dysfunction as determined by several laboratory tests [91] An acute pancreatitis may follow arterial disease of this organ In only a small number of patients with SLE is the spleen enlarged. In contrast, the

"onion skin" lesions of the vessels in the spleen may be detected microscopically in most instances It has been stated that the clinical phenomenon of hypersplenism may not be operative in SLE in spite of the development of hemolytic anemia, thrombocytopenia and other hematologic dysfunctions frequently attributed to this mechanism [24]

The incidence of lymphadenopathy in SLE varies from 32 per cent [74] to 67 per cent [44] The nodes may be enlarged in one anatomic area only, or there may be diffuse lymphadenopathy [10] Axillary, abdominal and thoracic adenopathy follow this order of involvement Lymph node hyperplasia is not associated with symptoms unless the node masses are of sufficient size to cause pressure Cervical lymph nodes may be as large as those seen in lymphoblastoma [82], may persist in the hypertrophied state for varying periods of time, and later break down with extrusion of necrotic material Abdominal lymphadenopathy may be accompanied by hypertrophy of the liver and spleen

Genitourinary Tract

Patients with lupus are particularly susceptible to urinary tract infection It is especially important to differentiate kidney involvement due to an infection that may respond to treatment from involvement associated with the basic morbid process Symptoms of renal impairment may be minimal, and clinical studies of the urine may not reflect the extent of damage that is observed microscopically at postmortem examination [53] One hundred per cent involvement of the kidneys was observed by Montgomery and McCreight [115] in a series of 32 cases of SLE They noted evidence of "renal irritation, nephrosis, or nephritis that was based upon a critical analysis of the various urinary findings" Miale [110] noted a galaxy of urinary findings : multaneously in patients with SLE or polyarteritis th: would be most unusual in patients with glomerulonephriti: These included red blood cells and red blood cell casts, ova fat bodies, fatty and waxy casts as well as albumin Albu-

minuria and hematuria may precede the development of skin lesions The ability to concentrate solids and to excrete phenolsulfonphthalein dye may be maintained in the presence of other evidence of renal dysfunction [59].

The clinical findings frequently are more suggestive of the nephrotic syndrome than they are of acute or chronic glomerulonephritis Anasarca, hypoalbuminemia, minimal change in blood pressure and proteinuria support this presumption An exception is the normal concentration of serum cholesterol Hypertension is uncommon in the early stages of SLE Advanced renal changes usually may be detected when the blood pressure is elevated The fear that adrenal steroids might produce renal disease or aggravate kidney dysfunction when used in treatment of SLE has not been substantiated Probably most patients at the present time who are known to be suffering from SLE receive a course of adrenal hormones The incidence of renal involvement does not appear to have increased during the past five years, as judged from a review of the literature

Central and Peripheral Nervous Systems

The incidence of central nervous system symptoms has been reported to be as high as 37 per cent [59] Haserick [62] noted that 11 patients in his series had received neuropsychiatric care prior to the recognition of organic manifestations One patient had exhibited central nervous system manifestations intermittently for 17 years prior to the confirmation of the diagnosis of SLE [59]. Convulsions, choreiform movements [107], aphasia, psychosis, meningismus [32] and paralysis have been assumed to be an integral component of SLE and not related to drug therapy, a complication of the disease, or a superimposed infection. Coma may be present in the terminal stages of the disease. Daly [27] described the development in one patient of a toxic delirium with irritability, restlessness, confusion and disorientation One case reported by Montgomery [115] complained of headache and facial palsy; papilledema was

demonstrated during opthalmoscopy In each case, endarteritis with partial occlusion of the cerebral vessels was noted at post-mortem examination

Convulsions in lupus may simulate idiopathic epilepsy and a diagnosis of grand mal has been made erroneously in several patients Seven out of 28 patients observed by Russell and associates [144] had convulsions The LE cell phenomenon was present in each instance A diagnosis of idiopathic epilepsy had been entertained in one patient two years before symptoms suggestive of SLE appeared In another patient epilepsy had been present for 16 years before the appearance of disseminated symptoms The electroencephalographic findings in eleven patients in this series showed normal tracings in only four In addition, abnormal tracings were demonstrated in two patients who failed to show central nervous system manifestations The electroencephalographic changes, unlike those seen in idopathic convulsive disorders, suggested organic brain disease Glaser [49] postulated that the vascular lesions show a predilection for the grey matter of the cerebral cortex, and would thus explain the convulsive seizures He also described disseminated encephalomalacia with hemorrhage or cyst formation which he believed to be secondary to vascular changes A tendency for convulsions to appear with exacerbations of the malady has been described

Examination of the peripheral nervous system may disclose increased activity of the deep reflexes, clonus and a positive Babinski Peripheral neuritis is a usual finding in polyarteritis but has been reported in some patients with SLE Paresthesias of the hands and feet, bilateral motor weakness, loss of light touch sensation, and impairment of vibratory sense have been observed [69] Piper [130] has reported an isolated observation of spinal cord involvement in SLE The patient died from a fulminating staphylococcus septicemia Paralysis of the lower extremities was associated with vascular changes and infarction of the meningeal vessels in the lumbar area of the spinal cord An increase in the protein

concentration, polymorphonuclear leukocytes and lymph-cytes in the spinal fluid have been noted. Abnormal spin fluid findings were discovered by Harvey and associates [59 in 10 out of 22 patients exhibiting signs of central nervou system involvement

Eyes

Conjunctivitis, episcleritis, embolic petechiae and corneal erosions have been observed upon direct inspection of the orbit [25, 74]. Approximately 30 per cent of patients with SLE show changes upon funduscopic examination These include exudates, hemorrhages, papilledema and central vein occlusion. Goldstein and Wexler [51] in 1932 described a case of SLE with optic atrophy, degeneration of the intima and media of the retinal vessels, and areas of retinal atrophy with replacement fibrosis. Baehr and associates [3] observed changes in the ocular fundus in 12 out of 23 cases Perivascular hemorrhages, fluffy exudates and, in two instances, papilledema were observed Blood pressure was normal in all except one of the patients The lesions were interpreted as due to vascular changes in the retina, and not to hypertension A short time later Kurz [95] described white patches in the fundus, retinal "cytoid bodies," which were believed to consist of ganglioform degeneration of nerve fibers Harvey believes that the presence of these lesions in the absence of hypertension or diabetes is highly suggestive of SLE.

There are no characteristic features of the retinal hemorrhages Usually they are small and located in the macular area or near the disc [109]. According to Koch and McGuire [90] the hemorrhages tend to be located in relatively avascular areas of the retina but in close proximity to the capillaries, the smaller venules and the arterioles A similarity to the changes in the fundus in patients with dermatomyositis and with polyarteritis was mentioned by these investigators Hyperemia, sclerosis, perivasculitis of the arteries, segmental periphlebitis and areas of complete replacement fibrosis of

veins and arteries are less constant findings in SLE [25] Retinal atrophy and retinal detachment have been reported by Rose and Pillsbury [111] Maumenee [109] studied microscopically the eyes from five cases of SLE and observed in each case the cytoid bodies in the retina which correspond to the yellowish-white or white spots seen in the fundus

LABORATORY FINDINGS

Red Blood Cells

A decrease in the number of circulating red blood cells is a significant laboratory finding in SLE [158] Baehr and associates [3] observed that "perhaps due to toxic damage to bone marrow, or to vascular lesions in the marrow, the blood picture usually reveals evidence of a depression in bone marrow function, leukopenia, thrombopenia, and a moderate anemia " Blood loss, kidney involvement, superimposed infection and anorexia—each may contribute to the development of anemia It usually is normocytic and normochromic, hemolytic in some instances The diminution in circulating red blood cells is not rapidly progressive, and in the absence of massive blood loss, severe azotemia, or a demonstrable hemolytic crisis, usually does not become profound

The development of hemolytic anemia in the clinical course of SLE or its appearance as the initial symptom in the malady has been reported by several observers [21, 31, 111, 131, 149] The features may include a marked decrease in hemoglobin concentration, reticulocytosis, hyperplasia of the spleen and a positive Coombs test Hypersplenism has been tentatively discarded by some as the explanation for the hemolytic anemia as noted above Coating of the red cells with an abnormal protein and subsequent destruction is believed to be a more likely explanation [59] Whether or not this abnormal protein is a true autoantibody is not known The Coombs' test in SLE may remain positive following a hematologic remission induced by cortisone therapy [131]

The erythrocyte sedimentation rate is increased [15] during the stage of acute manifestations and remains elevated during remission in many patients [124]. The frequency of transfusion reactions not attributed to ABO incompatibility has been noted [111]. Bone marrow examination shows normal activity except for an increase in the number of plasma cells The only correlation between degree of anemia and bone marrow findings is noted in patients with a hemolytic process Hyperplasia may be expected in such cases [15] Red blood cell agglutination has been reported by Evans and associates [14] in SLE as well as in patients with polyarteritis, dermatomyositis and scleroderma

White Blood Cells

A leukopenia usually is present [140] White blood cell counts below 2000 per cubic millimeter have been recorded [33] The values were less than 5000 in 71 per cent and 81 per cent of the cases, respectively, in two series reported from the Mayo Clinic [115] On the other hand, the response to infection may be a leukocytosis and a shift to the left in spite of the tendency to a leukopenia [111]. Any variation from the normal in the differential white blood cell count is toward an increase in neutrophils and granulocytes and a marked depression of lymphocytes [148] An eosinopenia [149] is more frequently observed than an eosinophilia. Eosinophilia sometimes follows steroid therapy [62].

Platelets

Purpura and petechiae have been associated with SLE since the early descriptions of the malady [80] Hemorrhagic vesicles and bullae which may involve the mucous membranes and extend into the gastrointestinal tract have been described The hemorrhagic manifestations have been associated with thrombocytopenia in some instances; in others, a normal platelet concentration has been observed. Thrombocytopenia was demonstrated in 9 out of 12 patients, and purpuric or petechial lesions were observed in 45 per cent of

the series described by Baehr and associates [3] Michael and associates [111] observed the incidence of thrombocytopenia to be slightly more than 50 per cent at some time in the course of the disease The Rumpel-Leede test has been positive in a number of patients

Idiopathic thrombocytopenic purpura has been the working diagnosis in several cases that were proven later to have lupus One or more years elapsed between the onset of purpura and the development of systemic manifestations suggestive of SLE [115] On the other hand, Damashek and Reingold [28] reported a case in which polyarthritis and a rash on the bridge of the nose and cheeks prompted a diagnosis of lupus five years before symptomatic thrombocytopenic purpura appeared As a result of a review of the cases following splenectomy for "idiopathic" thrombocytopenic purpura, it is believed that SLE should be excluded by an LE cell test in any patient suspected of suffering from the former malady [42, 59] Although splenectomy in SLE may be associated with clinical improvement and an increase in the number of platelets [75], some do not believe that hypersplenism is responsible for the deficiency in circulating platelets The relation of thrombotic thrombocytopenic purpura to SLE will be discussed later

Plasma Proteins

An increase in the globulin fraction, with or without a change in the albumin fraction, has been noted in a significant number of patients with SLE Hyperglobulinemia was present in 42 per cent of the series reported by Jessar and associates [74] Fifty-eight per cent of Harvey's cases, in which it was determined, exhibited a globulin concentration greater than 3 Gm per 100 ml with values recorded as high as 8 Gm The concentration of albumin in the serum was less than 3 5 Gm per 100 ml in approximately 50 per cent of this series, in several instances, it was less than 2 0 Gm The increase in the globulin fraction is restricted to gamma globulin, the alpha and beta concentrations are normal [26,

128] Exceptions have been reported by Hauser [66] and by Bille [15] who have observed an increase in the alpha-2 globulin fraction One patient with nephrotic manifestations and SLE revealed essentially an agammaglobulinemia [62] An increase in the serum fibrinogen content combined with the serum globulin changes contributes to the increase in erythrocyte sedimentation rate. In the absence of other evidence of involvement of the liver [91], the disturbance in plasma proteins is responsible for the false-positive flocculation tests for liver function Heterophile antibodies may be present in high concentration [148].

Serologic Tests for Syphilis

False-positive serologic tests for syphilis in SLE have been observed by many investigators since Gennerich [47] first reported this phenomenon. Alterations in serologic tests have preceded clinical symptoms of SLE in singular instances The observations of Haserick and Long [64] are notable in this regard They were fortunate in the opportunity to review the clinical records of five patients who had manifested false-positive tests for syphilis from one to seven years prior to the appearance of symptomatic evidence of SLE The incidence of false-positive tests in SLE is a function, among other factors, of the number of times that this is investigated per patient The data from the Mayo Clinic are illustrative The incidence of positive serologic tests in 30 patients with SLE prior to 1938 was 17 per cent. The incidence had increased to 44 per cent in 32 cases observed between 1938 and 1947 [115] The higher incidence in the second period was attributed to the greater number of tests performed per patient The experience of Coburn and Moore [22] was similar to that of the second period A positive reaction was noted in more than 35 per cent of 30 cases The Wassermann reaction was positive in eleven patients in their series while the Kline test was positive in thirteen Marked fluctuations in the titers from week to week were noted Globulin fractions were separated electrophoretically and

tested for activity with the Wassermann and Kline antigens The antibody was found to be principally in the gamma globulin fraction and was correlated only casually with the beta-2 fraction

The significance of the false-positive tests for syphilis in patients with SLE has been revealed by the preliminary observations of Moore [*117*], which have been brought up to date by Harvey and associates [*59*] and by Moore and Lutz [*116*] These observations will be reported in brief If the positive serologic test is suspected of being biologically false, a treponemal immobilization test [*122*] with a negative response confirms the false-positive presumption The biologic false-positive reactors may be divided into an acute and a chronic group The acute reactions occur during or immediately following infections from bacterial, viral, plasmodial or rickettsial microorganisms Reversion in the acute group occurs within a time period not longer than six months The chronic biologic false-positive reactors, on the other hand, have no antecedent acute infection that is presumed to be of etiologic significance, and the positive test persists The biologic false-positive reaction in the collagen dyscrasia is of this type In a series of 148 patients with chronic biologic false-positive reactions reported by Moore and Lutz [*116*], ten were suffering from well-developed SLE and seven from rheumatoid arthritis Clinical manifestations consistent with a diagnosis of SLE were demonstrated in forty-five of the remainder, but confirmation by laboratory tests was lacking A small number of patients exhibited positive LE cell tests, but the majority of the patients did not show this phenomenon If the components of these three groups are added, it will be apparent that nearly 50 per cent of the individuals in this study either suffered from clinical SLE or were potential victims of this malady Moore and Lutz considered the serologic and treponemal immobilization tests to be valuable tools for the study of the natural history of lupus It is postulated that the natural history of the disease as determined by the serologic response may be several years longer than cur-

rently is assumed. Prolonged study of biologic false-positive reactors and confirmation of these experimental observations undoubtedly will be of great help in the early recognition as well as in the understanding of this malady.

The LE Cell and the LE Rosette Phenomenon

One of the important advances in the understanding of this affliction was the discovery in 1948 by Hargraves, Richmond and Morton [57] of the LE cell in the bone marrow of patients suffering from SLE. This observation was confirmed shortly after by Haserick and Bortz [63]. It is appreciated now that the phenomenon may be demonstrated by mixing plasma from a patient with SLE and bone marrow elements from a normal subject, by mixing bone marrow or white cells of the peripheral blood from a patient suffering from SLE with plasma from a normal person, or it may be demonstrated in a smear of peripheral blood from an afflicted person. The phenomenon is produced by the reaction of a component in the plasma of a patient with SLE with formed elements of the blood or bone marrow. The origin of the formed elements is not relevant. The LE cell is a mature white blood cell comprising a homogenous reddish-purple staining inclusion body Although most LE cells are believed to be neutrophils, other types of leukocytes as well as lymphocytes may participate in the phenomenon. The inclusion body consists of partially depolymerized desoxyribose nucleic acid [96] derived from nuclear substances that formerly were integrates of neutrophils, lymphocytes or other cellular elements in the body. The altered nuclear substance is phagocytized by normal cells in the production of the LE cell The white cell balloons out in the process of phagocytosis, the segments of the nucleus are pushed to the periphery, and the remaining cytoplasm persists as a thin crescent surrounding the inclusion body (PLATE IV, page 2).

The LE rosette is the second characteristic phenomenon usually found in the same preparation as the LE cell. The rosettes are conglomerates of normal-appearing white blood

cells which surround a reddish-purple staining mass (PLATE V, page 3) Extracellular reddish-purple staining bodies which have not yet been the object of phagocytosis may be identified also The reddish-purple staining masses associated with the LE cells are believed to be identical to the hematoxylin-staining bodies described by Klemperer and associates [87]

There are at least three components necessary for the development of the LE cell and the LE rosette phenomenon [10] These are (1) A *plasma factor* associated with gamma globulin which is present in most patients with SLE This factor, which causes lysis of cell nuclei as manifest by swelling, homogenization and decreased staining reaction of the chromatin in the affected cells, is an immunologically distinct substance (2) *Nuclear material*, which is derived from the nuclei of the polymorphonuclear leukocytes The resultant of the reaction of the nuclear material and the LE fraction of the gamma globulin is chemotactic to phagocytic cells (3) *Phagocytic cells* (of indifferent source) complete the triad They cluster about the altered nuclear material and engulf it A single swollen phagocyte with engulfed material is the LE cell A cluster of cells about the lysed nuclear material comprises the rosette Of the three factors, the substance intimately associated with the gamma globulin fraction must be derived from a patient with SLE The phagocytic cells and nuclear material may come either from afflicted patients or from normal persons Obviously, several procedures may be employed in the preparation of material prior to the search for LE cells

Two additional factors contribute to the evolution of the LE cells Although the phenomenon may be demonstrated in the presence of anticoagulants, it is greatly accentuated by coagulation Secondly, the blood or bone marrow material must be maintained in vitro sufficiently long for the reaction responsible for the LE cell phenomenon to take place. Lee, Schwartz and Parisen [97] have shown recently that a fact derived from blood platelets may be necessary for the acti

tion of the LE cell. This may be identical with the LE cell cofactor, the "plasma thromboplastin" of Campbell and Stefanini [*18*] and the serum cofactor described by Kurnick [*94*]. The buffy coat of a sample of clotted blood is used generally in the search for LE cells, although blood to which an anticoagulant has been added may be satisfactory. Most important is the experience required by the microscopist. A considerable period of time should be consumed (30 to 60 minutes) before the search is abandoned, if SLE is suspected clinically. Repeated examinations may be necessary since the phenomenon may be exhibited intermittently in some patients. The LE cell factor may be demonstrated in body fluids other than the blood of patients with the malady. Such media include pleural, pericardial and cerebrospinal fluid, the contents of an experimentally inducted blister [*161*], and urine [*65*], respectively. The LE cell factor may cross the placental barrier. The LE cell phenomenon persisted in one infant for seven weeks after delivery from a mother with SLE, but was absent at the end of four months [*16*].

Demonstration of the LE cell phenomena is probably as specific a test as is available for the laboratory confirmation of a clinical diagnosis. The incidence of positive results as reported in the literature has varied from less than 50 per cent to virtually 100 per cent. The greater the number of times the test is applied in each suspected patient, the higher the percentage of positive findings. Furthermore, a repeatedly negative LE search does not exclude the diagnosis. Intensive study of selected patients with satisfactory clinical evidence of SLE has not revealed the LE cell phenomenon during life [*151*] even though the diagnosis has been confirmed microscopically at post-mortem examination. The persistence of the phenomenon is illustrated by the experience of Haserick [*61*]. The plasma of one patient with SLE induced a positive reaction in 47 consecutive bone marrow mixtures; that of another patient, in 46 consecutive attempts, and that of a third patient, in 36 attempts.

LE cells have been demonstrated in diseases other than

lupus in isolated and exceptional instances These have been judged to be false-positive tests Included in this list are single instances of military tuberculosis, pernicious anemia in relapse, leukemia, hemolytic anemia, multiple myeloma, amyloidosis, dermatitis herpetiformis and penicillin sensitivity Note should also be made of the SLE-like syndrome with demonstration of the LE cell phenomenon that has been induced during hydralazine therapy There are instances of the LE cell test turning positive during adrenal steroid therapy in patients with SLE [61] and following withdrawal of steroids This may represent progression of the disease rather than direct cause and effect Negative LE cell tests have been reported in a variety of conditions Harvey [59] lists more than 50 disease entities with negative results Scleroderma, polyarteritis, dermatomyositis, acute rheumatic fever and rheumatoid arthritis have shown negative results Strong suspicion should be entertained in favor of a diagnosis of SLE if a positive test is observed in a patient with a presumptive diagnosis of any one of these conditions

DIAGNOSIS

The increased recognition of SLE and the volume of literature during the past decade, out of proportion to the increased incidence of the disease, furnish tangible evidence of the importance of suspecting lupus in many patients with poorly defined symptoms and physical findings The critical physician will suspect SLE in a good many instances that will be proven subsequently to be some other malady Any patient with acute rheumatic fever or rheumatoid arthritis should be under some suspicion of developing SLE subsequently This is particularly applicable if atypical findings or an atypical course is noted Admittedly this is a radical concept but only by such an approach will more information become available regarding the natural history and other vital aspects of SLE so necessary to fill the void now existing Any female between 20 and 50 years of age with undiagnosed fever, malaise arthralgia, myalgia, either with or witho

skin lesions, should be under suspicion. Atypical forms of thrombocytopenic purpura, hemolytic anemia, glomerulonephritis, gastrointestinal bleeding, pleural or pericardial effusion, lymphadenopathy, epilepsy or toxic psychosis should be under suspicion also The finding of a false-positive serologic test for syphilis, a leukopenia and an elevated sedimentation rate should strengthen the suspicion.

The demonstration of the LE cell phenomenon in blood smears or bone marrow probably is the single most important diagnostic procedure If the clinical findings suggest SLE and the LE cell phenomenon is positive, there should be no doubt regarding the correct diagnosis. If repeated attempts to demonstrate this manifestation are unsuccessful, a biologic false-positive test for syphilis, confirmed by a treponemal immobilization test, may be almost as conclusive evidence [122] The microscopic examination of skin [39, 113], muscle, lymph node or kidney [102] removed at biopsy may be helpful Reliance need not be placed principally upon these procedures, since the recognition of the LE cell. The pathologic diagnosis at post-mortem examination includes changes in the connective tissue and the blood vessels particularly, the identification of the hematoxylin-staining bodies, the "onion skin" rings of the splenic arterioles, the "wire loop" lesions in the kidneys and the "cytoid bodies" in the retina. These subjects have been discussed in the section on PATHOLOGY

CLINICAL COURSE

The disease is fatal ultimately although the natural history sometimes covers a span of several years. Symptoms have persisted intermittently in exceptional cases over a period of as long as 20 years Ben-Ascher [12] reported the clinical course of one patient over a period of 23 years. The patient was alive and well at the time of the report This communication appeared prior to the discovery of the LE cell phenomenon There are no reliable prognostic criteria except a general one the more ill the patient, the more extensive the systemic involvement, the graver the prognosis Approxi-

mately 80 per cent of the patients in most series have died within five years after the onset of symptoms [74] Death within a year is not uncommon The course may be terminated fatally within a few weeks in patients afflicted with a rapidly fulminating type of the malady Spontaneous remissions not related to any specific therapy are relatively common The remission may last for months or even years, the patient meanwhile enjoys relatively satisfactory health Factors which may precipitate initial symptoms such as exposure to sun, infections and drug hypersensitivity are believed to contribute to a relapse Some patients may experience a second or yet a third remission Instances have been reported in which remissions have followed severe systemic involvement These are unusual, however Some observers have reported regression of symptoms following pregnancy The disease has not appeared to have been altered by this biologic event in other patients ACTH is the therapeutic agent of choice during pregnancy This is presumed to prevent adrenal depression in the fetus

Implications regarding the progression of the disease and the fatal termination have been modified somewhat during the past five years as a result of adrenal hormone therapy Undoubtedly periods of remission have been prolonged, relapses have been less critical, and complications either avoided or managed more satisfactorily with steroids Since most patients with clinical symptoms of SLE tend to be chronically ill and are unable to maintain adequate nutrition, the benefit from one of these therapeutic agents in correcting this disturbance may prolong life The antipyretic effect may contribute also The employment of antibiotics and the many advances of modern medical science, undoubtedly have been of value in preventing serious complications and in helping to maintain general well-being even though the ultimate course of the disease may not have been altered.

Death may be attributed directly to critical failure of one or more of the vital systems involved in SLE. Insufficiency

of the heart, kidneys or lungs, cerebral or gastrointestinal hemorrhage, and drug sensitivity have been reported as the immediate cause of death Fulminating sepsis was the commonest cause of death prior to 1935 It is less frequent now but remains an important factor. The following infections have been held responsible for a fatal termination in this current era of antibiotic drugs pulmonary tuberculosis, lobar and bronchial pneumonia, urinary tract infection, beta hemolytic streptococcal bacteremia, staphylococcal bacteremia and meningitis [160] It is fortunate that extensive employment of adrenal steroids in treatment has not been associated with an increase in incidence of a complicating or a terminal infection in SLE

TREATMENT

There is no cure for SLE; nevertheless, general measures as well as quasi-specific agents have proved to be of great help Nutrition should be maintained Physical rest during the acute phase of the disease usually is obligatory Heart failure should be treated with a low-salt intake and suitable cardiac preparations Sensitivity to the digitalis group of drugs has not been a therapeutic enigma Pain should be treated when it becomes a problem; opiates need not be withheld Transfusions have a place in the therapeutic regimen, especially if the patient has an anemia Mild or severe infections should be looked for carefully and repeatedly [159] If found, they should be treated with appropriate antibiotics Probably sulfonamides should be used only if other antibiotics are thought to be unsuitable. Penicillin has been under some suspicion because of the incidence of hypersensitivity following the use of this drug as well as the appearance of the LE cell associated with penicillin administration in exceptional instances in patients without SLE It has been noted repeatedly that antibiotics are ineffective unless the steroids are administered simultaneously. The indiscriminate use of drugs should be avoided. The parenteral administration of gold salts is condemned because of possible

harmful effects upon the kidney Particular attention should be given to the avoidance of exposure to the sun and artificial ultraviolet radiation because of the incidence of photosensitivity Some patients have learned that even a few minutes exposure may be harmful

The use of ACTH [52], cortisone, hydrocortisone, or prednisone offers the most promising temporary help that is currently available The mechanism of the beneficial effect of the adrenal hormones in the collagen disorders has not been elucidated Presumably it is related to suppression of harmful enzymatic processes in affected cells, rather than causing a reversal of the basic dysfunction Probably most patients in whom a diagnosis of SLE has been made have received one or more of the adrenal hormones It is believed that every patient with systemic symptoms in whom a diagnosis is strongly suspected or has been confirmed should receive adequate amounts of steroids, except as noted below The diagnosis of SLE usually is made upon hospitalized patients, and ACTH frequently is the first hormone given From 40 to 80 units of ACTH (Acthar-Gel) are recommended daily for a minimum of two or three weeks as determined by the criteria just stated From 40 to 80 mg of Hydrocortone is given daily in divided doses if this drug is selected Appropriately smaller amounts of prednisone may be prescribed Full therapeutic amounts of either ACTH or adrenal hormones are recommended for prolonged therapy This usually means from 10 to 20 units of Acthar-Gel daily, from 20 to 40 mg of Hydrocortone, or from 15 to 30 mg of prednisone in divided doses daily

✓The presence of active tuberculosis or cardiac failure has been judged to be a contraindication to steroid therapy in SLE A notable exception in the former situation has been reported by Johnson and Davey [76] They treated a patient with advanced cavernous pulmonary tuberculosis and SLE by means of streptomycin, para-amino salicylic acid and ACTH The signs and symptoms of lupus regressed, and the pulmonary infection became inactive Note should be made also of the potentialities of isoniazid Cardiac decompensation

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is not an absolute contraindication to steroid administration. The decreased sodium-retaining activity of prednisone is noteworthy. Furthermore, oral diuretics have been devised recently to supplement the action of digitalis preparations and a low salt diet

The dosage of adrenal steroids should be limited by the amount necessary to control symptoms, or failing this, up to the point of tolerance as determined by the development of symptoms indicative of Cushing's syndrome Proper attention should be given to a restricted salt intake if the larger amounts of ACTH or adrenal hormones are prescribed. Supplementary potassium, exchange resins and oral diuretics such as Neohydrin or Diamox are helpful in maintaining water and electrolyte equilibrium even though the patient does not suffer from demonstrable cardiac insufficiency. Most of the patients seen in our clinic are maintained on steroids so long as symptoms are present Less attention is given to sedimentation rate and white blood cell count as a guide to therapy It seems reasonable to us to attempt to control symptoms rather than to correct a hematologic or biochemical abnormality. There are some physicians who recommend intermittent adrenal hormone therapy. However, most of the communications in the literature have supported the continuous regimen The dosage is reduced progressively, and the minimum amount necessary to control symptoms is maintained, if a clinical remission occurs Sometimes a trial period without medication is instituted Steroids are resumed if symptoms return

A majority of patients will be benefited significantly by full doses of adrenal hormones A dramatic improvement may be noted frequently within a few days. General well-being is enhanced, there is an increase in appetite, a gain in weight, suppression of fever and an optimistic outlook, shared by patient and physician Regression of the cutaneous lesions during treatment has been observed in most patients. Lesions of recent appearance respond more quickly than long-standing chronic ones. Pigmentation has been reported following

prolonged steroid therapy. It has also been reported in patients with SLE who have not received steroids Considerable amelioration of joint symptoms may be expected Patients with pulmonary complaints experience subjective improvement There may be demonstrable evidence by x-ray of pleural or parenchymal clearing Significant relief from gastrointestinal distress may be anticipated Heart symptoms, not complicated by renal impairment, usually are ameliorated by steroids and appropriate cardiac agents Patients with pericarditis or cardiac failure may improve in spite of the tendency of the steroids to aggravate the latter state

Patients with demonstrable renal involvement usually show little or no improvement with steroids [*68*] Dubois [*35*], to the contrary, noted rather striking restoration in the function of the kidneys in selected patients A few with albuminuria and nitrogen retention showed normal findings following full doses of steroids There were two patients who developed evidence of nephropathy during treatment This cleared with increased dosage of steroids The effect upon central nervous system symptoms is more difficult to evaluate The incidence of convulsions, psychoses and other abnormalities in SLE is significant Furthermore, the incidence of psychoses during steroid therapy in other maladies is appreciable Russell and associates [*144*] observed a notable diminution in epileptiform seizures during steroid therapy in SLE Euphoria or minimal central nervous system irritability is not a contraindication to continuous administration of steroids A major central nervous system disorder usually is If central nervous system findings persist some time after discontinuing therapy, these should be attributed to the basic disease and not to treatment [*32*] The potential development of untoward reactions of steroid therapy, such as a duodenal ulcer, myocardial infarction, osteoporosis or occult infections, should not be overlooked

LE cells are diminished during a remission induced with steroids; and sometimes may disappear [*19*] Michael and associates [*111*] reported the appearance of LE cells in one

patient after cortisone had been administered, despite the fact that they had not been seen previously on repeated search of the blood and bone marrow. Their persistence in a significant number of patients who have experienced good symptomatic response is consistent with suppression of the malady but not the cure. Other laboratory evidence of alterations during therapy, in addition to the sedimentation rate and the LE cell phenomenon, is a partial restoration of the thrombocytopenia, leukopenia, anemia and eosinophilia. The altered albumin-globulin ratio has been observed to become more abnormal during steroid therapy [85].

Due to the variability of the disease—each patient reacting somewhat differently from the others—it is extremely difficult to draw valid conclusions regarding a significant effect upon prolongation of life with full doses of steroids. Most physicians would like to believe that steroids influence basically the course of the disease, in addition to an improvement for varying periods of time in the clinical picture. Nevertheless, statistic evidence which proves that the steroids alter the course of the disease by affecting any basic process that is an integral part of the mechanism of pathogenesis has not been forthcoming [35]. Kierland, Brunsting and O'Leary [84] reported post-mortem findings in one patient who had received ACTH and who had died with an uncontrolled infection of the peritoneal cavity. There was little evidence of lupus at post-mortem examination. It will probably take several more years, possibly another decade of observation, before highly suggestive or convincing evidence is produced. Meanwhile, the steroids have proved themselves, even though they are not specific.

The antimalarials are rapidly gaining favor in the treatment of SLE. Their use was suggested by the observations of Page [127], who reported the beneficial effect of mepacrine in 17 patients with chronic discoid lupus and in one patient with SLE. The observation that discoid lupus was benefited by quinacrine was made a decade before [132] but presumably was not applied to SLE at that time [34]. The value of

antimalarials is being studied in several clinics A few reports have been published The antimalarials have been used with and without adjunctive adrenal steroids A decrease in requirements for steroids has been observed while the antimalarials were administered The mode of action may be related to reduction in light sensitivity of the skin With the encouraging low incidence of side reactions, it is believed that these agents provide one more therapeutic approach to the management of this malady [31, 58, 84, 147]

Salicylates have been recommended for patients not believed to be suitable candidates for adrenal steroids Full doses should be administered and maintained at subtoxic levels for long periods of time, as in the treatment of acute rheumatic fever Salicylates also are of value in allaying the diffuse aches and pains as well as joint and muscle distress present in most patients

Nitrogen mustard and triethylene melamine have been used in selected instances A therapeutic trial in SLE was suggested by the clinical benefit reported in patients with glomerulonephritis Rohn and Bond [139] induced remission by these agents in three out of five patients with SLE for as long as 217 days Dubois [33] observed alleviation of anorexia in four out of five patients who were given nitrogen mustard and steroids Five out of six patients suffering from the dry state of nephrosis in SLE experienced improvement in systemic symptoms as well as improvement in kidney function Other drugs that have been recommended in the treatment of SLE include para-aminobenzoic acid [165], vitamin B_{12} [50], antibiotics and testosterone [141] Only temporary palliation in symptoms has been observed with each of these preparations

Polyarteritis

Polyarteritis (periarteritis nodosa) is a malady with protean clinical manifestations caused by widespread inflammatory changes in the walls of small arteries, arterioles, and occasionally veins. Although the older term, "periarteritis nodosa," is a relatively satisfactory designation, it has specific inherent disadvantages. The malady under consideration is more than "periarteritis," since the media and intima of the artery may be involved in addition to the adventitia Even "arteritis" is lacking in correct connotation, for capillaries and veins may be affected as well as arteries. Omission of "nodosa" has been advocated because nodular lesions are palpable in a minority of patients, and in the early stages of the disease should not be included as one of the essential diagnostic criteria Palpable nodules, in fact, are not critical components of the disease After inspection and rejection of the first as well as the second part of the term proposed by Kussmaul and Maier, others have been suggested as substitutes High in the preference list are polyarteritis, panarteritis and necrotizing angiitis, respectively. Polyarteritis (acute nodosa), suggested in 1903 by Ferrari [192], is believed to be the most acceptable substitute in current literature, and therefore will be retained for the malady under discussion.

Fibrinoid degeneration of medium-sized and small vessels throughout the body is an essential manifestation of this variety of collagen disorder The symptoms produced by the vascular damage are variegated and unpredictable, since they depend upon involvement of such vital structures as the kidneys, heart, gastrointestinal tract, and the several components

of the nervous system [93] Pathologic examination confirms the clinical impression that varying degrees of severity of arteritis may develop The entity described by Kussmaul and Maier [229] may have a prolonged clinical course associated with gastrointestinal symptoms, peripheral neuropathy and eosinophilia The larger vessels of the body tend to bear the maximum insult in this species Several stages of damage and repair may be detected concomitantly upon microscopic examination of affected structures In contrast, a rapidly progressive course may be observed in patients suffering from acute necrotizing angiitis The smaller vessels and capillaries, prone to be affected, show approximately the same stage of pathologic involvement Somewhere between these two variants, or possibly only casually related, is the polyarteritis that is confined to a single structure such as the appendix, gallbladder or uterus Removal of an organ so affected appears to mitigate against dissemination as well as result in a cure of the local process

There are several distantly related or even unrelated varieties of arteritis that will be mentioned in passing only These are temporal arteritis, generalized arteriosclerosis, serum sickness, Schonlein-Henoch purpura, erythema nodosum, acute glomerulonephritis, malignant hypertension with necrotizing arteriolitis terminally, and other maladies with extensive vascular lesions that have been classified by Zeck and associates [307, 309]

HISTORICAL

The nomenclature in this disease goes back less than a century, but pathologic descriptions are considerably older The designation, "periarteritis nodosa," was employed by Kussmaul and Maier in 1866 [229] in the description of a hitherto unnamed clinical entity with distinctive pathologic changes in the arteries The descriptive term referred to nodular lesions that were palpable under the skin of the chest and abdomen as well as visible along the larger arteries of the stomach, liver, spleen, lungs and heart at post-mortem



Fig 6—Reproduction of the drawing from the presentation by Rokitansky [277] showing multiple aneurysms of the mesenteric vessels

examination The nodules were aneurysms that were judged to be late effects of necrotizing lesions of the arterial tree. Approximately 200 years ago, Matani [241] published a monograph on aneurysms in which was included one case of multiple aneurysms of the coronary vessels. Most likely this was an example of polyarteritis Matani commented upon the failure of treatment in this malady. Less than two decades later (1785), Michaelis [249] reported what appears to have

been a similar case, as did Pelletan [*261*] in 1810. Rokitansky [*277*] is accredited with the first description of the minute alterations in structure Drawings of the gross findings (Fig 6) as well as camera lucida reproductions of the microscopic changes accompanied this communication, which was published in 1852 An excellent historical review of polyarteritis has been prepared by Diaz-Rivera and Miller [*187*], to which the interested are referred

INCIDENCE

Polyarteritis is not a clinical oddity [*250*] even though perusal of the current literature, particularly textbooks, tends to convey this impression Hospital record statistics have not been particularly helpful in the past in portraying incidence, since the disease has been detected in a significant percentage of cases by the pathologist from post-mortem material without a clinical suspicion. In 1914, Lamb [*230*] was able to assemble only 38 reported cases. In a review of medical literature a decade ago, Boyd [*172*] calculated that the incidence at that time was considerably greater than had been accepted A similar belief persists in some clinics today Supporting data have been supplied by Rich [*276*] He noted that the incidence of polyarteritis was only one in 1600 autopsies at the Johns Hopkins Hospital from 1916 to 1935 The incidence had increased to one in 137 autopsies in the period from 1936 through 1944

Polyarteritis is predominantly a disease of males, with a sex ratio that is approximately 3 1 The colored race is affected as well as the white race [*207*] Contratto [*184*] observed two Chinese students with polyarteritis who were temporary residents in the United States. The onset of symptoms usually begins at between twenty and fifty years of age However, instances in the young as well as in the old have been recorded Several cases have been reported in infants [*166*, *178*, *286*] Wilmer [*303*] observed one instance in the first 10 days of life and another at 37 days The diagnosis was made post-mortem in each case One of the oldest patients

reported in the literature was observed in the eighth decade of life [*258*]

RELATION TO OTHER COLLAGEN DISORDERS

Acute rheumatic fever [*304*], rheumatoid arthritis, and each of the unusual disorders discussed in this review have items of similarity to polyarteritis Ophuls [*260*] in 1923 suggested a close relationship of polyarteritis to the rheumatic processes because of a history of recent bouts of rheumatism or an onset following acute tonsillitis. This presumption was supported a decade later by the observations of Friedberg and Gross [*197*] Four out of eight cases of periarteritis nodosa (necrotizing angiitis) suffered from acute rheumatic fever or rheumatic valvular heart disease. Aschoff bodies were identified in the myocardium in each case. In another series of five patients with polyarteritis that were studied earlier [*290*], two had a rheumatic history and subsequent clinical evidence of rheumatic valvular disease. While these communications were in preparation, Middleton and McCarter [*250*] discussed the clinical and pathologic relationship between acute rheumatic fever and polyarteritis, an association believed to be greater than chance probability. One patient in our clinic with a past history of acute rheumatic fever and a clinical diagnosis of mitral stenosis developed generalized symptoms suggesting polyarteritis. A skin and muscle biopsy confirmed the diagnosis of polyarteritis The patient died approximately 18 months later Post-mortem examination showed the diffuse vascular lesions of polyarteritis as well as rheumatic mitral stenosis and a nonbacterial endocarditis

Arthralgia or articular symptoms suggestive of rheumatoid arthritis or SLE frequently appear early in the clinical course of polyarteritis [*199*, *224*] and may persist until death The anatomic diagnoses in one case discussed at the Massachusetts General Hospital included polyarteritis and rheumatoid arthritis [*232*] The anatomic diagnoses in another case included acute rheumatic fever, SLE and polyarteritis [*240*] The LE cell phenomenon was observed ante-mortem in this

patient. Aschoff nodules were demonstrated microscopically post-mortem The diffuse arterial lesions in rheumatoid arthritis may be distinguished from those of polyarteritis Photosensitivity [6] and a positive LE cell test [234], identifying features of SLE, have been noted in patients with polyarteritis Wire-loop lesions in the glomerulus were demonstrated by Symmers and Gillett [296] in a patient suffering from polyarteritis and thrombotic thrombocytopenic purpura. The histopathologic lesions in polyarteritis, SLE, dermatomyositis and scleroderma are similar, according to Pagel [357] Kampmeier and Shapiro [219] described one patient with polyarteritis who exhibited good clinical evidence of acute dermatomyositis, and at another time, SLE was suspected

ETIOLOGY AND PATHOGENESIS

Polyarteritis is the only dyscrasia in the group of collagen disorders under discussion that has permitted any clue regarding etiology or pathogenesis. Advancement of knowledge has not progressed beyond the stage of experimental investigation and clinical presumption, however, and it must be admitted that the etiology of polyarteritis in humans remains unknown Selected data believed to be significant point to the probability that the diffuse vascular lesions are manifestations of hypersensitivity In 1925, Gruber [208] published a critical review of the literature on periarteritis nodosa and stressed the definitive data concerning the pathogenesis of the malady He concluded that the changes in the tissues represented a general response most likely associated with hypersensitivity Gerlach [201] pursued a similar clue a few years earlier and reported necrosis of the arterioles at the site of the Arthus phenomenon

The definitive statements in 1935 by Kline and Young [227] concerning three cases of polyarteritis bear reproduction "In these three cases the picture suggests reactions to the same allergens as cause the usual clinical allergies The lesions which involve arterial walls particularly are appar-

ently due to allergic reactions in a highly sensitized body and are much more severe than those of the usual clinical allergies. The histologic changes in places are of the reversible type, but in many areas the tissues show marked irreversible degenerative and necrotic changes . . . Furthermore, reversible and irreversible changes similar to those in periarteritis nodosa have been observed in other tissues of the body in our material, especially in the appendix and gallbladder." In 1937, Clark and Kaplan [182] observed vascular lesions in the heart and testes of two patients who had died from serum sickness The resemblance of the vascular lesions to periarteritis nodosa was mentioned, but inferences relating pathogenesis to hypersensitivity were not pursued

Rich and Gregory [275] were the first in this country to produce polyarteritis in rabbits by the injection intravenously of large doses of horse serum and later horse serum together with sulfadiazine The lesions were similar pathologically to polyarteritis in humans These experimental studies followed the observation by Rich [272] of lesions of polyarteritis in the viscera of five patients who had suffered a hypersensitivity reaction following injections of horse serum that had been administered therapeutically There were also vascular changes in a section of muscle obtained at biopsy from a patient who had received sulfonamides and a foreign protein Experimental studies in rabbits were confirmed shortly after by Hopps and Wissler [214] Lesions of glomerulonephritis were also produced by the same experimental technic Free antigen remained in the blood stream after specific antibodies had developed

Various agents have been indicted as antigens and held responsible for the vascular lesions of polyarteritis in humans The sulfonamides were among the first in the group of agents that were implicated [205, 233, 273]. French and Weller [196] produced an eosinophilic interstitial myocarditis in rodents by the intraperitoneal injection of one of a number of sulfonamide drugs (neoprontisil, sulfanilamid, sodium sulfaypridine and sodium sulfathiazole) The pathologic

lesions were similar to those observed in the myocardium of patients who had received one of the sulfonamides shortly before death Gelfand and Aronott [*200*] investigated, by reference to hospital records, the relationship between the use of sulfonamides and the incidence of polyarteritis They discovered only four cases of polyarteritis in the records at Bellevue Hospital in the 20-year period prior to the introduction of sulfonamides in therapy Fourteen cases of polyarteritis were observed from 1938 to 1946, a ninefold increase per annum Mowrey and Lundberg [*256*] noted that all except three of the 320 cases from the Armed Forces Institute of Pathology were reported after 1939 More and associates [*253*] found evidence of "polyvasculitis" in 375 autopsies of patients who had received sulfonamides The vascular lesions were attributed to hypersensitivity. Significant histopathologic changes which suggested an individual susceptibility to sulfonamide drugs were reported by French [*195*] in material from 76 autopsies and two skin biopsies The drugs had been administered to some patients for only a few days before vascular changes were demonstrated Other drugs or noxious substances capable of producing hypersensitivity, and thereby implicated in the pathogenesis of polyarteritis include penicillin [*166*, *251*], Dilantin [*298*], poison oak and primrose [*280*], mercury [*198*], arsenicals [*252*], thiourea [*185*, *202*, *244*], iodine [*274*], cortisone and ACTH

These isolated and sporadic examples, however, do not appear to establish a consistent correlation clinically between the administration of any one drug and the development of symptoms of polyarteritis The exception is the antibiotics The mass of evidence concerning the antibiotics and the incidence of polyarteritis appears to the authors to support the hypersensitivity theory of pathogenesis of polyarteritis in humans Against these presumptions are the conclusions of Griffith and Vural [*207*] and those of Diaz-Rivera and Miller [*187*] Skepticism regarding a direct relationship between sulfonamide administration and the development of polyarteritis has been expressed in each instance Also Zeek

[*308*] assumed that the microscopic lesions in sulfonamide vasculitis were examples of "hypersensitivity angiitis," which could be distinguished from the changes of periarteritis nodosa.

The hypersensitivity hypothesis has received support from the clinical association of bronchial asthma and polyarteritis More than 15 years ago Rackemann and Greene [*269*] reported instances of periarteritis nodosa which appeared from one to 25 years after a clinical diagnosis of bronchial asthma had been made A search of the literature on periarteritis at that time revealed a 12 per cent incidence of bronchial asthma. Wilson and Alexander [*304*] reviewed 300 consecutive cases of polyarteritis in 1945, in which the incidence of bronchial asthma was 18 per cent Cases of urticar a, vasomotor rhinitis, and other expressions of atopy were encountered also, but were not included in the incidence datum Recently, Nuzum and Nuzum [*258*] calculated the incidence of bronchial asthma to be 25 per cent in a group of 175 cases of polyarteritis collected from the literature The symptoms of bronchial asthma usually preceded those of polyarteritis by only a few weeks. The pulmonary paroxysms tended to be severe and were related to intrinsic rather than extrinsic agents The average maximum eosinophilia in the peripheral blood was 53 per cent in the 44 cases of bronchial asthma and polyarteritis reviewed by Wilson and Alexander.

An interpretation of the pathogenesis of polyarteritis on an infectious basis has been proposed by several investigators. Seven patients in a series of 17 reported by Spiegel [*290*] in 1936 had infectious prodromata Acute tonsillitis, acute sinusitis, scarlet fever and acute rheumatic fever were the offenders Boyd [*172*] reviewed the records of 395 cases in the literature more than a decade ago and reported that one of a variety of infections appeared early in the course of the disease The usual childhood exanthemata, head colds and acute pharyngitis were included, as well as acute rheumatic fever, syphilis, malaria, influenza, scarlet fever, gonorrhea, typhoid fever and pneumonia. Polyarteritis has also followed

rat-bite fever [268] and postvaccinal hepatitis [263]. On the other hand, Griffith and Vural [207] were impressed only with the incidence of tonsillitis that preceded the development of polyarteritis in 17 cases reported from the Los Angeles County Hospital The serum antistreptolysin O and streptococcal antihyaluronidase titers were determined by Rantz, DiCaprio and Randall [134] in the pursuit of a streptococcal etiology in polyarteritis. Significant amounts of one or the other or both antibodies were detected in four out of five cases of polyarteritis, while high titers had developed in one It was concluded on the basis of these experimental studies that a preceding hemolytic streptococcal infection could not be excluded as the pathogenic agent. The relationship of a viral infection to polyarteritis has been considered [209] because of the identification of a vascular disease in lower animals, i e , the calf, pig, deer and dog [168] Against these presumptions is the experimental negative evidence from cultures, inoculations and attempted transmission to animals The angiotropic properties of viruses have not been proved by means of material obtained during life or at necropsy [174]

The association of hypertension and polyarteritis is believed to be more than coincidental [225, 254, 266, 302] Wilens and Glynn [302] calculated that the incidence of hypertension was approximately 60 per cent in a total of 28 cases of polyarteritis at the Bellevue Hospital and in 66 additional cases collected from the literature Hypertension preceded symptoms of generalized vascular disease in more than 10 per cent, and appeared at approximately the same time in 37 per cent The incidence of allergic reactions in the cases reviewed was higher in the nonhypertensive group However, the data suggested that polyarteritis developed more frequently in hypertensive nonallergic persons than in normotensive nonallergic persons Hypertension of the pulmonary arteries also has been implicated either as secondary to mitral stenosis [295], to congenital heart disease [225, 259], or in association with bronchial asthma

Experimental evidence in support of a hypertensive etiology has been reported from several laboratories Selye and Pentz [*284*] in 1943 noted that polyarteritis in rats could be produced by the combination of unilateral nephrectomy, administration of desoxycorticosterone acetate, and a high sodium chloride intake. A short time later Loomis [*236*] succeeded in producing hypertension and polyarteritis by infarction of the kidney. He noted that partial infarction was more likely to result in hypertension and vascular lesions than was total infarction Zeek and associates [*288*, *307*] have been the most recent advocates of a hypertensive etiology Their critical studies were based upon the production of hypertension and vascular lesions in rats by wrapping the kidney with silk. Various stages of vascular damage were demonstrated with a striking similarity in appearance microscopically to the lesion of polyarteritis in humans. The veins were affected by direct extension of the inflammation while the pulmonary circulation was spared. The observation suggested that polyarteritis is allied with a rapidly progressing hypertension.

PATHOLOGY

The vascular lesion that identifies polyarteritis is observed in the intermediate layer of medium and small caliber arteries. Each vessel coat, however, may be involved and veins as well as arteries may be affected, as noted above [*235*] There appears to be a preference for the bifurcation of medium caliber arteries at the point of origin of the vessels of decreasing size The necrotizing lesion may be confined to a small area of the vessel wall, or the entire circumference may be involved As the process spreads distally and proximally from the initial site, smaller and larger vessels may be afflicted. If the vasa vasorum of large vessels suffer, macroscopic aneurysms develop [*239*]. Nodosity may be produced by chronic periarterial inflammation and fibrosis or by aneurysm formation secondary to medial necrosis. Rupture with hemorrhage is always a threat following aneurysmal dilatation of the wall

Microscopically, segmental necrosis begins in the media and is accompanied by edema of the entire wall. Fibrinoid degeneration follows, with involvement of the inner elastic lamina associated with leukocytic and eosinophilic infiltration (PLATE VI, page 3). As the process progresses, it may extend through the intima into the lumen or peripherally to envelop the adventitia. Plasma cells, lymphocytes and monocytes may be seen in affected areas. Fibroblastic proliferation is a later manifestation. Various stages of inflammation and repair may be demonstrated. Healing with formation of scar tissue may be localized to a small section of the vascular wall, or the entire circumference may be encompassed. Thrombosis, recanalization and microscopic aneurysmal formation may be observed in adjacent sections (PLATE VII, page 4). When the entire circumference of the blood vessel has been involved, occlusion may be complete. The fibrous scar at this stage has lost its identity as an intimate part of a blood vessel.

Arkin [*168*] has divided the vascular lesions of polyarteritis into four stages. In the *degenerative* stage, arterioles without vasa vasorum show hyaline degeneration of the inner media. Also, there may be edema and fibrinous exudate in the subintima. The arteries with vasa vasorum show hyaline degeneration of the outer media proximal to the elastic externa. In the *inflammatory* stage, infiltration of the media and adventitia with polymorphonuclear neutrophils, lymphocytes and plasma cells may be observed. These changes may be associated with destruction of the inner media and of the elastica interna, with thrombosis, infarction and aneurysm formation. The third stage, i.e., *granulation*, is reparative. There is marked proliferation of fibroblasts from the adventitia into the inflammatory zone, a reduction in the number of polymorphonuclear leukocytes, and an increase in the number of lymphocytes, plasma cells and eosinophils. Recanalization may be disclosed in this stage. The damaged arterial wall is replaced by a fibrous scar with reduction or obliteration of the lumen in the fourth or *healed* stage (PLATE VIII, page 4).

According to Arkin, a close relationship exists between pathologic lesions of the last three stages and the clini- manifestations of polyarteritis. The degenerative e may be silent clinically. The initial symptoms appear .e inflammatory stage and mimic either a severe or a low- e infection Organic manifestations of varying degree location occur as a consequence of thrombosis, infarction, .rysm formation and hemorrhage. Cachexia and emacia- may be observed in the stage of granulation, if involve- t is widespread Kussmaul and Maier decribed this as cosmus The persistence of symptoms following regres- of fever may be related to progressive reduction of the d supply in the organs severely affected. A partial remis- ensues if extensive healing is permitted. The severity of disease and persistence of clinical symptoms is also a tion of collateral blood supply. The organs with end- ies tend to show the greatest degree of permanent dam- following vascular involvement [238].

Statistic studies of organ involvement have revealed the ey to be most susceptible. The kidneys were afflicted in er cent of the 230 cases reviewed by Mowrey and Lund- [256]. Harris and associates [210] found the kidneys e involved in 87 per cent in a series of cases The heart wed the kidneys in order of susceptibility in each series r organs affected included the adrenals, pancreas, liver, n, testes, gastrointestinal tract and brain. The lungs were lved in approximately 25 per cent of autopsied cases s examination of the lungs may give little hint regarding presence of diffuse vascular disease. Microscopically, the chial arteries may show the various stages of deteriora- with an appearance similar to the vascular changes in affected portions of the body.

CLINICAL FINDINGS

A detailed description of the clinical picture will be nted, but there is no characteristic group of symptoms clinical findings representative of this dyscrasia Indi-

vidual manifestations are extremely varied, particularly in the early stages and sometimes in the later stages as well The other collagen disorders discussed in this monograph present several features individually that are helpful in suspecting the underlying disturbance The symptoms and clinical findings of polyarteritis may be extremely elusive.

In order to emphasize the fallibility of segregating the identifying features that appear at the onset of the malady, Boyd [172] tabulated the provisional diagnosis of 50 patients upon entry to the hospital who were later found to have polyarteritis General infections headed the group. These included acute rheumatic fever, typhoid fever and brucellosis Abdominal symptoms which suggested cholecystitis, peritonitis and other serious maladies below the diaphragm shared second place with musculoskeletal phenomena which included trichinosis, polyneuritis and myositis Cutaneous disorders and cardiac dyscrasias followed in this order. Central nervous system disorders appeared last

The presenting symptoms sometimes suggest the diagnosis of arthritis, rheumatism, myositis or neuritis [238]. The patient may complain of a low-grade fever, weight loss, palpitation, abdominal pain, weakness, dyspnea, cough, vomiting, headache or visual disturbances The distress or indisposition is so subtle as to provide little or no helpful clue, and the onset so insidious as to justify the assumption that extensive pathologic changes have been present for a period of time before medical help is sought Pain, a prominent symptom, may be localized or diffuse This has been attributed by Horne and associates [215] to the combination of damaged blood vessels and hypertension It was noted that pain was absent in one case when the blood pressure was normal and present when the pressure was elevated

On physical examination, a skin eruption may be apparent as well as pallor, tachycardia, hypertension, sensory changes and emaciation The incidence of fever in patients with this malady varies from 70 to 100 per cent [187, 210, 218, 279] It usually is low-grade and may be continuous or

intermittent in periods lasting several days or even several weeks The fever may follow a septic pattern and be out of proportion to the apparent severity of the patient's illness Sweating may be profuse Shaking chills are unusual in the absence of a demonstrable infection, although chilliness is a frequent complaint Tachycardia likewise may be out of proportion to the elevation of temperature.

The symptoms and physical findings in the several systems of the body will be discussed separately, although they may develop concomitantly Several clinical forms have been differentiated, and several "types" of polyarteritis have been described in detail in an effort to emphasize the dominant symptomatology, i e , gastrointestinal, renal, neuromuscular, cardiac and cutaneous. Such a division as noted above is believed to serve no useful purpose.

Kidneys

The vessels of the kidney are affected in most patients, and clinical findings emanating from involvement of these organs are to be expected Fourteen out of 30 patients studied by Ralston and Kvale [*270*] had renal symptoms in the following order of frequency: intermittent or persistent pain in the lumbar region, nocturia, dysuria, gross hematuria, anuria and incontinence The significance of routine urine analyses in the evaluation of renal involvement was emphasized. Although renal symptoms were present in only 45 per cent of the patients in this series, abnormal urinary findings were detected in 89 per cent In three out of 20 cases in which hypertension was present, an elevation of blood pressure suggested renal involvement in spite of the inability to demonstrate microscopically vascular changes in the kidney. Conversely, only 17 developed hypertension among 24 cases with vascular lesions in the kidney. The opinion was expressed that, although hypertension usually is accompanied by vascular changes in the kidney, it may be the result of a diffuse obliterative process of nonrenal vessels in patients without demonstrable renal involvement Griffith and Vural [*207*]

observed hypertension in 13 out of 14 patients who showed vascular changes in the kidney. The experience of Wilens and Glynn [*302*] has been noted above. A rapid elevation of blood pressure and the presence of renal damage has been interpreted as a grave prognostic sign [*187*]

Renal failure is a frequent cause of death Gruber [*208*] reported such a terminal incident in 25 per cent in a survey of 100 cases. Several instances have been reported of death following rupture of an aneurysm of the interlobular arteries of the kidney with formation of a perirenal hematoma [*301*] The shadow cast by such a mass has been mistaken for a renal tumor [*278*] Gross pathologic findings in the kidneys and surrounding structures in polyarteritis include infarction, nephrosclerosis, glomerulonephritis, perirenal and retroperitoneal hemorrhage and hydronephrosis with infection Fisher and Howard [*194*] observed moderate dilatation with spasticity of the upper third of both ureters at two examinations of a 13-year-old girl who suffered from acute abdominal complaints Post-mortem examination performed six weeks after onset of symptoms revealed polyarteritis of the kidneys, ureters and gallbladder A review of the literature by these investigators failed to reveal a similar case description

Heart

The myocardium may bear the brunt of the insult followed by vascular changes in the pericardium or endocardium Secondary involvement of the heart muscle may be expected if hypertension is persistent or severe Pathologic findings in the heart were demonstrated by Griffith and Vural [*207*] in a majority of their cases. while evidence of focal polyarteritis was present in less than 50 per cent of the series The coronary vessels and the small vessels of the myocardium showed lesions which resulted in myocardial fibrosis and fibrinous pericarditis but only infrequently in myocardial infarction There was a relatively high incidence of coronary arteriosclerosis and left ventricular hypertrophy in this series The review by Mowrey and Lundberg [*256*] revealed that

enlargement of the heart was frequently associated with hypertension, that cardiac murmurs were not of diagnostic significance and that congestive heart failure was the most common cause of death Angina pectoris was an uncommon complaint in the history, in spite of the fact that 58 per cent of the cases showed involvement of the coronary arteries. Murmurs, usually systolic in time, are present if the endocardium is affected.

There are several reports in the literature which indicate a higher incidence of coronary involvement in children with polyarteritis than in adults [*166*, *265*]. The coronary lesions were responsible for death in a case of a child reported by Stryker [*292*], while diffuse systemic involvement was limited to minimal intimal proliferation of the cerebral vessels and lesions in the kidney that suggested glomerulonephritis Sinclair and Nitsch [*286*] reported one case of polyarteritis in a child in which the vascular lesions were confined to the coronary vessels The two cases with aneurysmal dilatation of the coronary arteries reported by Diaz-Rivera and Miller [*187*] were the youngest in their group An aneurysm in one patient ruptured into the pericardial cavity and caused death from tamponade. Massive thrombosis of the coronary arteries was responsible for death in the other child

Gastrointestinal System

The gastrointestinal tract frequently is the locus of complaints and is responsible for the initial manifestations of polyarteritis referred to this system. Pain, tenderness and cramps—localized or generalized in the abdomen—nausea, vomiting, distension, diarrhea or melena may suggest an acute abdominal condition The epigastrium or right upper quadrant is more often the site of symptoms if they are localized Surgical exploration may seem indicated [*167*] for suspected intestinal obstruction, acute appendicitis, a penetrating ulcer, a bleeding ulcer or a malignancy. Seven out of 15 cases in the series of Spiegel [*290*] suffered from surgical

complications which involved the gastrointestinal tract Observers have commented upon the poor correlation between abdominal symptoms and microscopic findings of polyarteritis Wold and Baggenstoss [*306*] reported that 37 per cent of a group of 21 cases showed involvement of the vessels of the jejunum This was followed in frequency by lesions in the ileum, colon, stomach, duodenum, rectosigmoid, and lastly, the appendix Infarcts, hemorrhages, ulcerations, perforations and peritonitis have been observed at post-mortem examination following extensive vascular disease of the blood vessels that supply the gastrointestinal tract Acute ulcerative enteritis or colitis [*217*, *299*] and intussusception have been reported Felsen [*191*] discussed an interesting finding that he observed during sigmoidoscopy Direct inspection of the large bowel revealed dark red parallel streaks separated by healthy mucosa and shown subsequently to be thrombosed vessels associated with polyarteritis

The liver, gallbladder, pancreas or spleen may be afflicted by the vascular process Symptoms from hepatic involvement may suggest acute cholecystitis, a common duct stone, hepatitis or cirrhosis of the liver The liver may be involved primarily with widespread vascular lesions, or it may be secondarily affected from cardiac failure. Infarction of the liver, thrombosis, hemorrhage, necrosis, and inflammatory infiltration have been reported [*243*, *266*, *306*] An increase in amount of fibrous connective tissue of the liver together with bile duct proliferation may result in the appearance grossly of Laennec s cirrhosis Symptoms indicative of primary liver damage are less frequent than is the incidence of microscopic findings at post-mortem examination Mowrey and Lundberg [*256*] discussed 10 examples of liver involvement among 200 cases that had been reported in the English literature and added 16 cases from the records in the Armed Forces Institute of Pathology The incidence in each group was less than 5 per cent Griffith and Vural [*207*] presented one case of an infarction of the liver secondarily infected, with subsequent rupture of the abscess into the peritoneum

Vascular changes in the gallbladder may be suspected from symptoms of acute cholecystitis [208], or they may be observed incidentally by the pathologist, as in the case reported by Allen [167]. Two cases similar to this have been seen in our clinic. The pancreas may be the site of acute vascular changes [207, 291]. Pancreatitis with fatty degeneration [262] and diabetes mellitus [193] have been observed in polyarteritis.

Lungs

Complaints referable to the lungs are apt to be minimal or absent, except for those patients with a history of bronchial asthma who subsequently develop clinical manifestations of the diffuse vascular process. Chronic cough, bloody sputum and pleuritic pain unrelated to bronchial asthma have been reported in case histories [294]. In a series of 19 patients with polyarteritis studied by Doub and associates [188] pulmonary symptoms were highest in those whose course was a rapidly fulminating one. Seven of the nine cases in this series that were examined post-mortem showed lesions in the pulmonary or bronchial arteries. Microscopic changes in the parenchyma of the lung were more prevalent than was the incidence of pulmonary symptoms. The incidence of pathologic findings may be as high as 25 per cent. Sandler [282] described pulmonary cavitation in one patient which resulted from extensive parenchymatous infarction due to polyarteritis. One patient with localized pulmonary lesions that suggested an abscess by x-ray has been followed by a physician in our clinic for more than four years (Figs. 7, 8, 9). Removal of one lesion at the beginning of the period of observation revealed microscopic changes typical of polyarteritis. A similar lesion appeared in the opposite lung two years later. The patient meanwhile has been maintained on steroids. Lesions in the pulmonary circulation frequently are associated with hypertension [295, 308]. When atelectasis, pleural effusion, empyema, bronchopneumonia, lobar pneu-

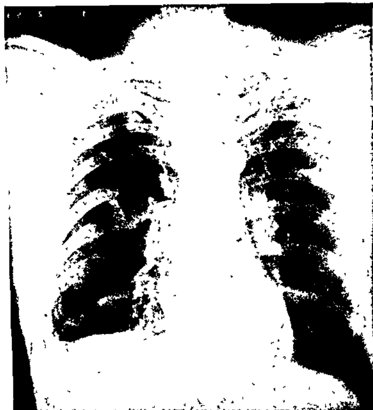


FIG 7—Roentgenogram of the chest taken in 1953 of a patient with polyarteritis A routine x-ray of the chest was negative in 1947 Pulmonary symptoms began in 1951 at which time a lesion in the right lung was detected by x-ray This was removed and the microscopic diagnosis was polyarteritis This x-ray taken in 1953 shows a small lesion in the left lung (See FIGS 8 and 9)

monia and emboli appear, it is believed that they should be considered as complications secondary to the underlying vascular lesions [*207, 243*]

The high incidence of pulmonary lesions in patients classified by Zeek [*308*] as "hypersensitive angiitis" and by Churg and Strauss [*181*] as "allergic granulomatous angiitis"

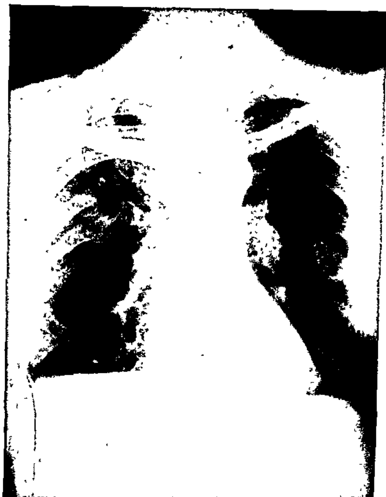


Fig 8—Roentgenogram of the chest taken in 1954, of the same patient as in Fig 7 The large cystic lesion on the left lung is similar to the lesion that was removed from the right lung three years earlier Well-developed clinical symptoms of polyarteritis had appeared in the meantime A skin and muscle biopsy was positive for polyarteritis



Fig 9—Roentgenogram of the chest taken in 1955 of the same patient as in Figs 7 and 8 The lesion in the left lung is smaller The patient had been on steroids for many months

is noteworthy Vascular lesions in two cases studied by Zeek were limited to the pulmonary circulation. A necrotizing pneumonia was present in three cases. Characteristic changes by roentgenography were lacking. Kipkie and Johnson [225] reported a case of polyarteritis confined to the pulmonary arteries in an 11-year-old boy with subacute glomerulonephritis and congenital heart disease No other arteries of the body were involved; even the bronchial arteries were spared Old and Russell [259] reported two cases of polyarteritis limited to the pulmonary arteries. Hermann [211] and Griffith and Vural [207] reported one instance each of polyarteritis with involvement of the bronchial and pulmonary arteries Whether or not these instances are typical of polyarteritis or belong to a variant of this dyscrasia is not settled

The association of bronchial asthma and polyarteritis was one of the first observations in contemporary medicine which suggested that the pathogenesis of this morbid state was a function of hypersensitivity. Bronchial asthma in these patients appeared to be the "garden-variety" type that presented no unusual features prior to the development of vascular disease Many of the patients with bronchial asthma who have developed polyarteritis exhibit an intrinsic or nonatopic variety of hypersensitivity. It is unusual for extrinsic allergens to be identified as etiologic factors. A maximum eosinophilia which ranged from 11 to 84 per cent and averaged more than 50 per cent was present in many of the cases reviewed by Wilson and Alexander [304]. On the other hand, in a control series of 151 cases of polyarteritis without clinical symptoms of bronchial asthma, the eosinophilia was not greater than 6 per cent and averaged less than 3 per cent. A suspicion of polyarteritis should be entertained in any patient afflicted with bronchial asthma who reveals an eosinophilia greater than 15 per cent, according to these observers It should be noted in concluding this discussion of pulmonary findings that empiric observations suggest a grave prognosis in patients with respiratory complaints

Central and Peripheral Nervous Systems

Central nervous system symptoms or a peripheral neuropathy may usher in the clinical phase of the disease In other patients, nervous tissue appears to be involved only terminally The diagnostic possibility of polyarteritis may be overlooked unless additional systems of the body produce symptoms Personality change, headache, speech impairment, diminution of vision, cerebellar signs, vertigo, lethargy, convulsions, delirium, weakness, facial and ocular palsy, paralysis of the extremities and deep reflex changes, as well as acute ascending paralysis of the Landry's type, have been described in polyarteritis Parker and Kernohan [262] reviewed the clinical and pathologic findings relative to the central nervous system in 16 patients who had died of polyarteritis Symptoms that indicated involvement of the central nervous system were present in seven during the clinical course before terminal developments Four showed evidence of central nervous system involvement in the terminal stages only Two of the seven patients in the first category suffered from multiple cerebral abscesses, and three showed a diffuse neuronitis Several stages of vascular involvement were observed microscopically The vertebral, carotid, meningeal, cerebral and the deeper arteries of the brain shared in the process

Boyd [173], in a review of the literature, observed a higher incidence of meningeal involvement in younger individuals This was manifested either by generalized or by Jacksonian convulsions Combination forms with meningoencephalitis as well as primary meningitis [228] have been noted One patient studied by Griffith and Vural [207] was admitted to a contagious disease service because of headache, nuchal rigidity, aphasia, hemianopsia and flaccid hemiplegia Necropsy showed polyarteritis of the circle of Willis, the cerebral cortex and subcortex Typical lesions of polyarteritis were demonstrated also in the cerebral arteries of two patients who were admitted with profound central nervous sys-

tem symptoms. The basilar artery was involved in one case observed by Diaz-Rivera and Miller [187]. A rupture of an aneurysm was the terminal incident. Another case showed arterial occlusion from thrombosis which led to infarction of the right frontal lobe. Complete bilateral nerve deafness from eighth cranial nerve lesions was reported by McNeil and associates [246]

Approximately 50 per cent of patients with polyarteritis exhibit signs or symptoms of peripheral neuritis. Paresthesias, weakness, tenderness of the nerve trunks, muscle paralysis, loss of deep reflexes, brachial plexus involvement [223], wrist drop and foot drop [256] have been reported. Peripheral neuritis developed several months after the onset of symptoms in many of the patients in the series reported by Lovshin and Kernohan [237]. Motor changes overshadowed the sensory changes The onset of peripheral nerve involvement may be abrupt or insidious. It may afflict one or several nerves and encompass one or more extremities The distribution shows a lack of symmetry and follows no characteristic pattern of dissemination Upper and lower extremities are involved with the same frequency. Temporary regression of the peripheral neuritis has been observed The clinical picture in one case reported by Griffith and Vural [207] suggested multiple neuritis Necropsy revealed vascular lesions of polyarteritis in the cerebral vessels also. Kernohan and Waltman [220] observed one patient, a 54-year-old male, who showed vascular lesions post-mortem that were limited to the nerve trunks of the upper and lower extremities and to the capsule of the prostate

Lovshin and Kernohan [237] examined microscopically approximately 100 nerves from 25 cases of polyarteritis. Vascular lesions of the nutrient arteries were demonstrated in 76 per cent and nerve degeneration in 44 per cent of the specimens Symptoms of neuritis were recorded in the history of each patient who showed involvement of the nutrient arteries at post-mortem examination The microscopic changes were similar to those seen in the other arteries in the body. A re-

duction in the caliber of the lumen with subsequent diminution of blood supply appeared to be the principal functional defect The small arteries in the interfascicular connective tissue showed the highest incidence of involvement The veins were spared. Diverse sections of the vessels showed marked variations in the degree of the inflammatory process Nerve degeneration, typically Wallerian, was severe in the distal portions of the nerve and minimal at the levels of vascular damage, with imperceptible evidence of inflammation in the nerve fibers Infarcts at the level of the vascular lesions appeared beneath the epineurium, in some instances situated deep within the fasciculi

Eyes

There is considerable difference of opinion in the literature regarding the incidence of ocular lesions in polyarteritis It has been estimated to be as low as 20 per cent and as high as 75 per cent The examination of the eyegrounds is not mentioned in a number of case reports, and precise conclusions regarding the frequency of affliction as determined by this examination are not possible In spite of this deficiency, polyarteritis is believed to have more types of ocular manifestations than has any other collagen disease Hollenhorst and Henderson [*212*], in a comprehensive review of this subject, outlined five ocular disorders in polyarteritis as follows: (1) Direct involvement of the medium and small vessels may be observed on ophthalmoscopy Vascular lesions of the choroid are visible as globular edematous areas with fairly well defined borders If these changes are extensive, they may result in detachment of the retina Occlusion of the central artery of the retina, silent lesions of the ciliary artery, scleritis, tenonitis, involvement of the orbital arterioles, arterial involvement of the ocular muscles, massive intraocular hemorrhage and exophthalmos are included in this group (2) Exudative lesions may follow involvement of mesenchymal tissue Edema of the eyelids, conjunctiva and cornea, as well as iridocyclitis, result from this process (3) Involvement of

the cerebral vessels may lead to extraocular muscle palsy, pupillomotor disturbance and homonymous hemianopsia Edema of the optic disc due either to toxic retinopathy or to increased intracranial pressure, ischemic neuritis or hypertension may be present. (4) Characteristic hypertensive retinopathy from extensive vascular changes in the kidney results in spasticity of the vessels, hemorrhages, exudates, edema of the disc and retinal detachment. (5) Toxic retinopathy is associated with changes similar to those described in malignant hypertension

Krohulik and associates [*228*] believe that the ocular vessels are subject to less acute degenerative and inflammatory features than are the vessels in other organs, and that the eye changes may be summed up as those of subacute and chronic uveitis, episcleritis and orbital cellulitis According to Goar and Smith [*204*], polyarteritis manifests itself by thickening of the vessel wall with diminution of the lumen or edema, transudate, hemorrhage and cytoid body formation The changes in the vessel wall are considered to be typical of polyarteritis, the other findings are presumed to be the result of renal involvement and hypertension. Characteristic changes are more often found in the choroid, but the retinal, ciliary, muscular and episcleral arterial branches may be affected also Other ocular manifestations in polyarteritis include iritis [*179*], retinal vein thrombosis with sudden loss of vision [*202*, *213*], acute anterior uveitis, infiltration of the corneoscleroconjunction and corneal ulcers with a disagreeable necrotic odor [*305*].

Muscles and Joints

Muscle, joint and tendon involvement may be responsible *for the initial symptoms Muscle tenderness* may be secondary to involvement of the nerves that supply the muscles or may be related to vascular lesions within the muscle fibers The myositis may be sufficiently acute as to suggest trichinosis [*229*] or acute dermatomyositis The affliction may be localized, or it may spread to each of the four ex-

tremities Symptoms of joint disease are probably related to the vascular lesions in the synovial and capsular tissues Arthralgia, rather than arthritis, is a better designation in a majority of instances Symptoms tend to be low-grade and fleeting, and bear only a casual resemblance to acute or chronic arthritis Arthralgia or myalgia was present in each of 12 patients reported by McCall and Pennock [*243*]. On the other hand, joint swelling was observed in only two instances Friedman and colleagues [*199*] reported that arthritis or myositis was present in seven out of eight cases of polyarteritis They suggested a classification of the joint manifestations into three major groups (1) myalgias and arthralgias, (2) acute and subacute polyarthritis; and (3) chronic progressive deforming polyarthritis In the latter category, the clinical findings may be indistinguishable from chronic deforming rheumatoid arthritis Lowman [*238*] noted that muscle tenderness and arthralgia were present in 30 out of 43 patients in the earlier stages of polyarteritis The myositis was aggravated by activity and improved by rest The arthralgias, usually migratory, were not associated with periarticular swelling There was objective evidence of swelling in only four cases Microscopic study of synovia disclosed arterial lesions similar to those in other tissues of the body, with spotty synovial changes secondary and proportional to arterial lesions Muscle or joint symptoms preceded the development of peripheral neuropathy in 19 out of 30 cases Roentgenographic examination of joints usually discloses no specific alterations except osteoporosis, which has been attributed to diminution of blood supply [*200*]

Skin

Approximately 25 per cent of patients with polyarteritis show cutaneous manifestations [*287*] The disorder has been reported to be limited to the skin in some instances; in others, the cutaneous manifestations may be the presenting findings [*228*] A more favorable prognosis has been reported if well-developed skin manifestations are present. The lesions in-

clude erythema multiforme [271], dermatitis gangrenosa [203], livedo racemosa, livedo reticularis [221], neurodermatitis, ulcerations of the buccal mucosa [281], necrotic lesions [243], urticaria, bullae, hemorrhagic purpura, bronzing, pigmentation, papules and subcutaneous nodules, respectively Capillaries and smaller vessels of the cutis as well as those in the subcutaneous fat may show characteristic changes of polyarteritis The process may lead to ischemia, degeneration, necrosis, infarction or hemorrhage. Involvement of the larger arteries may result in gangrene and mutilation

Subcutaneous nodules have been recognized for almost a century as an important clinical finding in polyarteritis If they are detected, removed by biopsy and examined microscopically, the diagnosis is confirmed. Subcutaneous nodules on vessel walls are late manifestations, however, and are observed in a small percentage of patients only. They were present in only two out of 17 cases reported by Griffith and Vural [207] They may be located on the extremities, chest, abdomen, face, back, scalp, scrotum or tongue. They may occur in crops, are painless, and may persist for a short time only. The dimensions range from one or two millimeters, which may be hardly detectable on palpation, to a centimeter or more in diameter If hemorrhage is associated with rupture of the aneurysm, the nodule may be several centimeters in diameter They may vary considerably in size along a single blood vessel Crops of nodules accompanied by fever and prostration have been reported

Endocrine Glands

The endocrine glands appear to escape the pathologic process in many patients, or at least clinical evidence of endocrine lesions is not usual except for the testes Involvement of the testicular arteries and veins with pain and swelling has been reported by a number of investigators [235, 213, 251]. Orchitis due to infarction is an unusual episode Adrenal arterioles have been affected with complete vessel occlu-

sion, phlebitis and periphlebitis The literature contained no reports of lesions of the thyroid or pituitary

LABORATORY FINDINGS

Examination of the urine usually reveals abnormal constituents McCall and Pennock [*243*] reported abnormal urine findings in each of 12 cases of polyarteritis. Ralston and Kvale [*270*] reported albuminuria, red cells in the sediment and granular or hyaline casts in 25 out of 28 patients. A similar high incidence was noted by Griffith and Vural [*207*] Special features of the abnormal urine findings were investigated by Krupp [*92*] in 21 patients The presence of red and white blood cells, red blood cell casts, oval fatty bodies, fatty casts and abnormal quantities of protein, respectively, was demonstrated in each instance The term telescopic sediment was used by Cole [*183*] to describe these findings These several abnormalities in their entirety are not reported usually in cases of glomerulonephritis or in other common renal disturbances [*248*]. The observations of Schreiner [*283*] are the exception He described telescopic urinary sediment in three instances of typical glomerulonephritis and concluded that this phenomenon was not pathognomonic of polyarteritis or SLE

A decrease in renal efficiency may be detected by the function tests and by an increased concentration of blood urea nitrogen Polyuria, fixation of specific gravity, decreased phenolsulfonphthalein excretion and progressive azotemia may be present The blood urea nitrogen concentration was greater than 60 mg per 100 ml in 16 out of 24 cases reviewed by Ralston and Kvale [*270*] The concentration was greater than 100 mg in 12 instances Azotemia may be observed as a terminal event in some patients

A mild normocytic hypochromic anemia may develop in the absence of gross blood loss The anemia is not so severe as the pallor would suggest. The finding of a red blood cell count below 2,000,000 is unusual The white blood cell count tends to be increased but may be normal or even de-

creased There may be an increase in percentage of polymorphonuclear cells, with a shift to the left An eosinophilia —transient or persistent—may be of considerable aid in diagnosis Percentages as high as 75 per cent with a total white blood cell count of more than 25,000 have been reported An eosinophilia of 90 per cent seems to be the record [174] The incidence of eosinophilia is higher in patients with bronchial asthma and in those with an extended clinical course Blackburn [171] reported one example of an elevated eosinophile count and an abnormal bone marrow that were highly suggestive of eosinophilic leukemia. The characteristic findings of polyarteritis were recognized at necropsy. Bone marrow studies have shown an eosinophilia, an increase in reticulocytes and a leukopenia. Griesbacher [206] considered these findings to be helpful in the diagnosis The fragility of the red blood cells and the bleeding time are normal. Prolonged clotting times and positive tourniquet tests have been reported in a few patients. The sedimentation rate usually is increased.

A decrease in total serum protein and reversal of the albumin–globulin ratio may be present [198] False-positive tests for syphilis, and LE cells in the blood have been observed [208, 235] Lepow and associates [231] investigated a spontaneous precipitable protein which appeared after cooling of the serum for 24 hours at 4° C The protein was unlike cryoglobulin, since it did not redissolve at room temperature Electrophoretic studies have shown that it belonged to the gamma globulin fraction This is not exclusively a feature of polyarteritis and has been observed in patients with other maladies who have shown a reversal of the albumin–globulin ratio A positive precipitin test for trichinosis in a dilution of 1:1280 was reported by Gelfand and Aronoff [200] in three out of five cases of polyarteritis. *Spinal fluid findings include an increase in pressure*, a slight increase in the protein content, an increase in the number of polymorphonuclear cells or lymphocytes, and the presence of xanthochromic fluid [207, 228]

Electrocardiographic abnormalities comprise low-voltage, inverted T waves, RS-T changes and bundle branch block Griffith and Vural [*207*] observed abnormal electrocardiograms in ten out of eleven patients with polyarteritis The abnormalities included sinus tachycardia, low-voltage, prolonged QT interval, left axis deviation, abnormal T1, T2, and T3 waves, and auricular fibrillation Serial electrocardiograms in four cases with clinical evidence of coronary involvement [*235*] showed progressive coronary insufficiency

Roentgenographic examination of the chest usually is negative; significant findings have been noted in a small number of patients [*170, 188*] Minimal involvement included slight prominence of linear markings throughout the lungs, and in some instances, small localized densities More advanced changes have been revealed as hilar enlargement, extension of haziness out from the hilum, perivascular and parenchymal infiltration, fibrosis, bronchiectasis and cavitation The upper lobes and the bases are particularly susceptible to pathologic changes Patchy infiltration tends to clear, only to become involved a second time Herrmann [*211*] pointed out the value of serial roentgenograms of the lungs in patients with polyarteritis

DIAGNOSIS

Consideration of the possibility of polyarteritis in any undiagnosed bizarre condition is to be encouraged Males in the middle decades of life, who are obviously ill with multiple complaints, should be under suspicion Hypertension, eosinophilia, hematuria, peripheral neuropathy, abdominal symptoms and an intermittent fever, respectively, may furnish a clue The diagnosis should be suspected in a relatively high percentage of cases in the late stages of the disease Although the diagnosis has been made post-mortem by the pathologist many times in the past in cases without a correct clinical presumption, sagacious experience together with the appreciation of the incidence of this disease surely will improve the ante-mortem percentage The goal is a high per-

centage of correct diagnoses in the early stages of the affliction Unquestionably, this is asking a great deal. and probably will not be achieved until a laboratory examination is devised that is as reliable as the LE cell test in SLE. Arthralgia, muscle pain, malaise and a low-grade fever are not particularly helpful clues Nevertheless, only one or two of such symptoms may be present for a period of time before the patient becomes "ill" and more alarming signs or symptoms develop If the diagnosis were suspected and confirmed at the onset of symptoms, it is hoped that the clinical course might be prolonged or altered significantly [*189*].

Confirmation of suspicion at the present time rests upon a positive skin or muscle biopsy. Vascular changes may be demonstrated if polyarteritis is responsible for the symptoms and meager laboratory findings. The lesions may be observed in skeletal muscles that are neither tender, atrophied nor weakened No one area of the body is preferred for biopsy unless cutaneous or subcutaneous involvement is apparent clinically Occasionally the areas selected for biopsy may have escaped the vascular process Maxeiner and associates [*242*], *in a recent survey, have reported a rather discouraging* series of results Positive results were recorded in only 13 per cent of 136 muscle biopsies from 106 patients suspected of suffering from polyarteritis The biopsies were positive in only 30 per cent of the 26 patients who were proven subsequently to have polyarteritis Three consecutive biopsies failed to show specific microscopic changes in one case reported by Solomon and associates [*289*], although autopsy examination disclosed typical polyarteritis Other observers have not reported so disappointing an experience, and a generous portion of skin and muscle for microscopic examination *remains the most reliable laboratory* confirmation of a case suspected clinically of polyarteritis.

The subdivisions of polyarteritis or related angiitides, according to the classification of Zeek and associates, present a difficult problem in differential diagnosis. *Hypersensitive angiitis* [*308*] follows the clinical features of an infectious

process associated with sensitivity to selected therapeutic agents Renal failure is a common cause of death Post-mortem examination in this dyscrasia reveals widespread involvement of lungs and follicular arteries of the spleen. Fibrinoid necrosis may involve the entire vessel wall with an intense cellular reaction. The vascular lesions appear to be in the same stage of exudative reaction and show little evidence of healing *Allergic granulomatous angiitis* [*181*, *299*, *308*], which includes asthma and Loeffler's pneumonia, appears as a hypersensitivity phenomenon caused by various allergens Recurrent episodes of pneumonia may be observed, while heart failure is a common cause of death The allergic granuloma may be observed within the vessel wall as well as in connective tissue throughout the body, as a result of necrosis of eosinophils, fibrinoid degeneration in the connective tissue, and granulomatous proliferation of epithelioid and giant cells *Temporal* or *cranial* arteritis [*222*, *247*] affects females in the later decades of life Frequently it is self-limited, benign in its course, and characterized by low-grade fever, generalized weakness and tender or painful areas over the scalp and along the course of the involved arteries Microscopic nodules of granulomatous infiltration with foreign body giant cells may be highly suggestive but are not pathognomonic *Focal arteritis* of the appendix [*267*] has been observed in slightly more than one per cent of more than 6000 [illegible] the incidence highest in [illegible] est an acute abdominal [illegible] follows appendectomy

CLINICAL COURSE

Fulminating polyarteritis usually is fatal within a period of from four to 12 months after the appearance of clinical symptoms [*216*, *218*, *270*] Diaz-Rivera and Miller [*187*] observed the average duration of life to be 50 days in six patients suffering from the rapidly progressing form Only 20 patients lived longer than one year in a series of 152 cases reviewed by Boyd [*174*] The duration was less than

three weeks in 15 patients. Caution must be exercised in evaluating such short histories because of the unreliability of properly interpreting time of onset of symptoms

There are several reported instances of patients living in apparent good health for several years, even a decade or more, the diagnosis having been confirmed by a positive biopsy [*175*, *210*, *224*, *226*] These are exceptional instances and usually represent arteritis confined to a relatively small area of the body not essential for life, such as the gallbladder, appendix or uterus. Kampmeier and Shapiro [*219*] *observed one patient with polyarteritis for 21 years* Acute arterial changes were discovered in the appendix removed in 1932 Necrotizing arteritis was present in biopsied muscle tissue removed subsequently in 1948 and in 1950 Post-mortem examination in 1953 revealed acute necrotizing arteritis in a section of rectus muscle, but no arterial lesions in the healing stage were discovered

Signs or symptoms of involvement of the central nervous system, renal system or cardiopulmonary system should be interpreted as ominous Post-mortem examination in some instances reveals less extensive involvement than would be anticipated but for the fatal outcome. This paradox has given rise to the suspicion that the insult to the body may be something in addition to mechanical interference with circulation and alteration of normal metabolic processes in the areas supplied by the damaged vessels.

TREATMENT

Supportive measures only are of value High in this list are the adrenal hormones, cortisone, hydrocortisone and prednisone and ACTH, respectively. Opiates or sedatives should be prescribed for persistent acute pain or for sedation *The disease in many instances produces emaciation;* hence, a high caloric, high vitamin diet is to be recommended Whole blood transfusions may be helpful if anemia is present The employment of antihistaminics in treatment, because of the association of polyarteritis and hypersensitivity

in selected patients, has resulted in significant improvement in a few cases Since cessation of contact with an offending antigen may be beneficial, a careful search should be made for a sensitizing antigen Antibiotics have been employed on the assumption that bacterial organisms were associated with the etiologic mechanism [287] Even sulfonamide drugs, that are believed to be contraindicated on the basis of the observations of several investigators, have been used with considerable benefit [205] Para aminobenzoic acid [*177*, *245*] and neoarsphenamine [255] have been credited with clinical improvement.

Surgical interruption of sympathetic impulses has been carried out in a few instances, particularly in those with hypertension This procedure has been advocated on the presumption that lowering of the pressure will diminish vasculitis A sympathectomy was performed in one case reported by Symmers and Litchfield [297] Tissue removed at the first stage of a bilateral sympathectomy showed acute vascular lesions The patient died shortly after the second stage, which was 25 days after the first operation. All sections examined post-mortem showed healed lesions or evidence of rapid progression of the healing process. A more satisfactory result was reported by Horne and associates [*215*] in a patient subjected to splanchnicectomy The patient was in good health at the last report, six years following surgery.

The antipyretic and appetite-stimulating effects of the adrenal hormones, with improvement in general well-being, may be temporary but frequently are highly beneficial There is little evidence from clinical experience or from a review of the literature that one adrenal steroid is preferred to another in treatment Cortisone and ACTH appear to have produced essentially similar results The advantage of the cortisone preparations is that they may be taken by mouth There is hope that prednisone will prove more satisfactory than cortisone or hydrocortisone Although the effects of the steroids are temporary in most instances, suppression of some

of the clinical manifestations has been reported as well as inhibition of progression of vascular lesions [*169*, *297*].

Microscopic evidence of improvement following steroid therapy has been noted by Lincoln and Richter [*234*]. The diagnosis of polyarteritis in this instance was confirmed by muscle biopsy. Large doses of cortisone resulted in dramatic clinical improvement A second muscle biopsy six months later showed normal architecture. The remission continued at the time of the report, one year after beginning treatment Simpson and associates [*285*] reported one patient with cutaneous, abdominal and kidney manifestations. The diagnosis of polyarteritis was confirmed at biopsy. A remission was induced with ACTH Sixteen months after beginning treatment the patient was reported to be symptom-free. Minimal skin changes and minimal albuminuria persisted Weller [*300*] observed a young girl with a rash, nodules, microscopic hematuria and a positive biopsy whose general symptoms responded promptly to ACTH The nodules subsided, the serum proteins became normal, but the rash persisted Dent and associates [*186*] reported the instance of a boy with cutaneous and abdominal symptoms Clinical regression followed administration of antibiotics, but a remission followed the administration of cortisone A biopsy at the beginning of treatment showed the typical vascular lesions of polyarteritis. A surgical specimen (appendix), which was removed during cortisone administration, showed evidence of healed polyarteritis. The patient continued to be symptom-free two years later. A similar case has been reported by Carey, Harvey and Howard [*176*]. The number of cases that respond favorably to steroids is discouragingly small The disease in most patients continues without abatement except for temporary symptomatic treatment. Relapses appear shortly after the drug is discontinued in some patients who experience complete or partial remission during steroid therapy [*180*, *257*].

Drury and associates [*189*] considered cortisone a potentially lethal agent which has produced ominous visceral

infarctions and death, meanwhile exerting a favorable influence upon the affected vessels locally. Zeek cautions against the use of steroids in the rapidly fulminating type of necrotizing angiitis Ehrenreich and Olmstead [*190*] reported the development of malignant hypertension in a patient who had received 600 mg of cortisone over a period of three days only A causal relation between the administration of cortisone and the development of malignant nephrosclerosis, as disclosed by autopsy, was suggested Potential harm to the kidneys from the steroids may be suspected on the basis of experimental studies by Rich and associates [*276*] ACTH and cortisone inhibited the development of proliferative glomerular lesions during the development of polyarteritis in rabbits following administration of horse serum Continued administration of ACTH was associated with maintenance of normal glomerular structure Cortisone, on the other hand, induced severe hemorrhagic glomerular damage similar to that of acute glomerulonephritis in humans However grim these reports are, the possible development of these undesirable effects may not be a contraindication to treatment [*297*]

Dermatomyositis

DERMATOMYOSITIS is a dyscrasia of multiform nature usually associated with cutaneous lesions (Plate IX, page 5), extensive muscle weakness and muscle tenderness. The onset of the morbid condition may be acute, with severe and rapidly progressive *peripheral and visceral symptoms, or it may* become manifest in a comparatively mild form with low-grade symptoms and subsequently progress rather slowly Incomplete remissions have been observed in some patients A complete remission is most unusual Removal of a tumor has been followed by disappearance of symptoms of the collagen disorder in the small number of patients in whom dermatomyositis has been associated with a malignant neoplasm. Residual muscle inflammation, skin atrophy and secondary joint changes in the chronic stage may lead to disability. The

in most cases of acute dermatomyositis is fatal within a period of from one to three years Morbid involvement of one or more vital systems may be the immediate cause of death

HISTORICAL

One of the first clinical descriptions of acute dermatomyositis in contemporary literature is attributed to Wagner [376] In 1887, he described a 34-year-old female with painful muscles and joints and weakness of the shoulder girdle who died a few weeks after she was first seen A case described by him [375] a quarter of a century earlier as acute polymyositis is believed to have been incorrectly diagnosed [338] and

probably was trichinosis Hepp [331] used the term pseudotrichinosis in a description of a case of dermatomyositis, while Unverricht [374] described the condition as polymyositis acute progressiva. Jackson [333] re-reported Hepp's case the same year (1887) in the *Boston Medical and Surgical Journal*. Three years later Unverricht proposed the term, "dermatomyositis." Oppenheim [356] was the first to emphasize the similarity of dermatomyositis and progressive scleroderma. Steiner [369] in 1905 reported one of the first cases recognized in America

Other terms which have been used historically to describe this condition include polymyositis hemorrhagica, dematomucomyositis, neuromyositis, dermatoneuromyositis and angiomyositis Since most clinicians and pathologists are familiar with the designation, "acute dermatomyositis." the authors believe that this term should be retained even though cutaneous lesions are not so persistent nor so distressing as the myositis Acute dermatomyositis refers to the clinically active stage of the disease The significance of the progression in some patients to a chronic stage with leathery skin, advanced muscle wasting, disabling joint changes, subcutaneous calcinosis, inanition and incapacity, i e , a clinical state similar to chronic systemic scleroderma, presents a debatable issue [360] Since the issue is, in part, one of semantics, it cannot be resolved to the satisfaction of interested persons in the present stage of our knowledge concerning these disturbances

The presence of extravasated blood, as noted in the histologic examination of the skin, is considered to be a manifestation of generalized dermatomyositis The observation does not justify the subclassification of polydermatomyositis hemorrhagica [335] Poikiloderma atrophicans vascularis has been considered by some dermatologists to be a malady closely related to dermatomyositis. Muscle weakness and systemic symptoms, however, are absent in the former condition The disorder is primarily a cutaneous one, with certain similarities in the histologic changes of the skin [321] In poikiloderma, the epidermis is decreased over the papules only; in

dermatomyositis, the thinning is general. The connective tissue shows little alteration in poikiloderma. The term, "poikilodermatomyositis with calcinosis," has been applied to cases reported by Horn [*433*] and by Silva and associates [*366*] The clinical and morphologic findings are essentially the same as in dermatomyositis with calcinosis.

INCIDENCE

This is not a rare malady. An increased appreciation of the potential incidence of the disease is responsible for the diagnosis being suspected more often than formerly, and the diagnostic criteria pursued earlier in the course of those presumed to be afflicted on the basis of clinical findings A review of our experience, which is confined largely to patients admitted to the medical service in a general hospital, reveals that the incidence of acute dermatomyositis ranks second to SLE among the unusual collagen dyscrasias.

The highest incidence appears to be in the fourth and fifth decades of life Curtis and associates [*316*] reported that the ages varied from 20 to 69 years in a series of 45 patients observed at the University Hospital in Ann Arbor, Michigan One case has been reported by Wainger and Lever [*377*] of a 76-year-old male who died three months after the onset of swelling and weakness of the arms. *Post-mortem examination* revealed a carcinoma of the stomach in addition to characteristic changes of dermatomyositis in the skeletal muscles The incidence in children [*329*] of acute dermatomyositis is *higher than that of any of the other collagen disorders* under discussion Karelitz and Welt [*336*] collected 75 cases of dermatomyositis from the literature in 1932, and noted that 22 were children Demel [*318*] reported one case of dermato*myositis in the first week after birth* Wedgewood and associates [*378*] reported 26 cases in children between two and 11 years of age The malady was fatal in 40 per cent of this group of cases Six of the 26 cases had been in a remission and *symptom-free for more than two years* They also reported

seven instances of the acute phase changing into the chronic atrophic form with calcinosis

Females tend to be more susceptible, the ratio is approximately 3/2 in adults [354] and in children [378] A contrary experience has been reported by Keil [80], who stated that dermatomyositis was *more* likely to appear in males Dermatomyositis in mirror-image female twins has been reported by Wedgewood [378]. Symptoms in one twin began one year before the onset in the other The one who developed the disease first had minimal involvement, while the other had a more severe form The biopsy findings in each instance were characteristic The disease has been reported from all parts of the world Several patients have been Negroes [338]

RELATION TO OTHER COLLAGEN DISORDERS

The symptoms and clinical findings suggestive of acute rheumatic fever may be present for weeks or months before acute dermatomyositis is suspected These include fever, migratory polyarthralgia, tachycardia and electrocardiographic changes An acute pharyngitis may precede systemic symptoms Undoubtedly, acute rheumatic fever and acute dermatomyositis may coexist, although the burden of proof rests upon the proponent of such a possibility in each instance

Kellogg and Cunha [337] reported pertinent data on a young female with acute dermatomyositis confirmed by biopsy Six years before onset of symptoms of dermatomyositis she had a bout of migratory polyarthritis A clinical diagnosis of mitral stenosis based upon satisfactory evidence was made at a later time Symptoms of acute dermatomyositis developed without a recrudescence of acute rheumatic fever O'Leary and Waisman [354] reported two instances of rheumatic heart disease in a series of 40 cases of dermatomyositis. A 36-year-old female in our clinic was under treatment for several weeks with clinical findings indistinguishable from acute rheumatic fever The persistence of fever and malaise, however, raised some suspicion regarding the validity of this diagnosis Muscle weakness and pain about the shoulder girdle



FIG 10.—Roentgenogram of the hand of a patient with acute dermatomyositis The symptoms initially suggested rheumatoid arthritis There is periarticular swelling of the proximal phalangeal joints and diminution of joint spaces

appeared approximately two months after onset of articular symptoms A skin and muscle biopsy showed changes believed to be characteristic of dermatomyositis. The clinical course during the following three years substantiated this diagnosis, nor did later eventualities lend credence to a diagnosis of acute rheumatic fever or of rheumatic valvular heart

disease Apparently this was another instance of acute dermatomyositis masquerading as acute rheumatic fever initially.

A clinical diagnosis of rheumatoid arthritis is more apt to be entertained if the patient has articular distress in the early months or even years following onset of symptoms of dermatomyositis Swelling of the proximal phalangeal joints (FIG 10), subluxation, ulnar deviation of the hands and periarticular swelling with effusion of the knees leaves little doubt regarding a presumptive diagnosis of rheumatoid arthritis [*315*] In seven out of 25 cases of dermatomyositis, Ragan [*358*] reported joint stiffness and periarticular swelling In three he found characteristic changes of rheumatoid arthritis Patients with extensive muscle involvement from dermatomyositis with symptoms persisting for a year or longer have shown demineralization similar to that in advanced arthritis O'Leary [*353*] noted that fixation of joints and muscular contractures in dermatomyositis occurred more frequently in children severely afflicted

We have under treatment a 52-year-old housewife who displayed typical findings of "rheumatoid arthritis" for 15 months before a skin and muscle biopsy was performed There was little to controvert a clinical diagnosis of mild rheumatoid arthritis at the time of the biopsy, except for progressive muscular weakness out of proportion to articular changes In spite of minimal cutaneous manifestations, the pathologist considered the microscopic changes in muscle as well as in skin to be typical of acute dermatomyositis During the 18 months that she was on adrenal steroids, the patient improved considerably

The similarity of clinical findings in SLE and in acute dermatomyositis suggests a close relationship Differentiation is possible in most instances, however [*80*] Among the clinical phenomena that may be encountered in either dyscrasia are fever, muscle and joint pains, mucocutaneous lesions [*364*], alopecia [*40*, *312*], photosensitivity [*373*, *381*], vasospastic symptoms of Raynaud's syndrome, purpura,

lymphadenopathy, splenomegaly, leukopenia and renal involvement Edema about the eyes and of the face usually suggests acute dermatomyositis. Large muscle groups are prone to be involved in this malady. Patches of erythema may be observed over muscle masses that appear to be acutely affected upon clinical examination. We have seen one patient, a 31-year-old female, who gave a history of having had a butterfly rash on her face following exposure to the sun This was diagnosed as "lupus" by an experienced dermatologist Several months later generalized symptoms appeared Approximately two years later a skin and muscle biopsy showed changes characteristic of dermatomyositis. The patient died seven years after the appearance of the butterfly rash A search for LE cells in the blood, not made early in the course of the disease, when it was performed terminally, proved negative. Another patient, a 22-year-old girl, gave a story of intermittent arthralgia and sensitivity to sunlight On numerous occasions a rash on exposed areas of the body would appear within a few minutes after exposure to the sun. A skin and muscle biopsy, 18 months after the onset of generalized symptoms showed changes characteristic of dermatomyositis Subcutaneous nodules became palpable one year later, with evidence of diffuse calcinosis demonstrable upon x-ray examination.

Several physicians believe that dermatomyositis and systemic scleroderma are the same disease, or at least they assume the basic features to be identical Included in this group are Allan [*310*], Dowling and Griffiths [*332*], Kinney and Maher [*338*], Langmead [*340*], O'Leary [*354*], Rothstein and Welt [*360*] and Rudolph [*361*]. The pathologic process in either malady involves the skin, muscles and blood vessels widely scattered throughout the body [*325*]. Edema of the face may appear early in either malady, followed by minimal to advanced skin changes Wainger and Lever [*377*] have postulated that collagen degeneration is severe in dermatomyositis and produces a profound inflammatory reaction On the other hand, the degeneration in scleroderma is mild, and

results in minimal evidence of inflammation but extensive and pronounced fibrosis Allan [310] reported the case of a 46-year-old male who had edema of the skin followed by atrophy and clinical symptoms of scleroderma The biopsy report showed changes characteristic of dermatomyositis in the skin and muscle. This patient experienced an almost complete recovery at the end of five years Brock [312] has enumerated several features helpful in distinguishing dermatomyositis from scleroderma Facial edema, proximal muscle involvement, muscle pains and erythema of the skin usually are present in acute dermatomyositis Joint symptoms, vasomotor disturbances and distal muscle involvement have a higher incidence in generalized scleroderma Brock believes, however, that a diagnosis of scleroderma is justified if subcutaneous calcification develops in the chronic state, irrespective of whether the diagnosis was dermatomyositis at an earlier time Against this conviction is the knowledge that an appreciable number of well-documented cases of dermatomyositis develop extensive calcinosis after a period of one or more years [310, 321, 354, 358]

NEOPLASTIC DISEASE AND DERMATOMYOSITIS

The incidence of malignant tumors in dermatomyositis is considerably higher than chance [315] In one of the earliest reports of this association, Sterz [370] observed a patient with dermatomyositis and carcinoma of the stomach Credit is given in the recent literature to Bezecny [311] for emphasizing the coexistence of the two conditions His experience with dermatomyositis included two examples of carcinoma of the ovary and one example of carcinoma of the breast He postulated that the "tumor toxins" were responsible for the musculocutaneous disorder The symptoms attributed to dermatomyositis improved temporarily following surgery in two of the patients Fifteen years ago O'Leary and Waisman [354] reported an incidence of 5/per cent malignancy in patients with dermatomyositis The recent datum of 18-per cent in the series at Ann Arbor [316] is believed to be more

representative Carcinoma of the ovary and of the breast appear more frequently than do other tumors [323]. Presumably this is a function of the sex incidence of dermatomyositis and the frequency of malignancy of the primary and secondary sex organs in females Brunner [314] reported the coexistence of dermatomyositis and malignancy in a 47-year-old female Cutaneous and systemic symptoms of determatomyositis together with a positive muscle biopsy confirmed this diagnosis ten months before the development of abdominal swelling. An anaplastic carcinoma of the ovary was discovered at exploratory laparotomy. The cutaneous lesions of dermatomyositis subsided following a three-month period of x-ray therapy of the tumor. A papillary carcinoma of the ovary was discovered in a patient reported by Forman [324]. It had been removed seven years before the onset of symptoms of dermatomyositis This latter diagnosis was confirmed by a skin and muscle biopsy.

Simpson [368] reported a case of carcinoma of the breast which appeared six years before the development of clinical evidence of acute dermatomyositis. Two additional cases of dermatomyositis and carcinoma in females were presented in the discussion of this communication Necropsy of two cases of dermatomyositis as reported by Sheard [363] revealed a tumor in each instance The ovary was the primary site in a female aged 46 A well encapsulated carcinoma of the gallbladder was discovered in the second patient, a male 53 years of age Metastases had appeared in each case. Wilson [380] reported that one of his patients had a local mastectomy nine years before the onset of muscle weakness. A scirrhous carcinoma of the breast appeared subsequently, and was treated by a radical mastectomy, four years before the diagnosis of dermatomyositis was suspected. This clinical diagnosis was confirmed later by a biopsy. Carcinoma of the lung, esophagus, stomach, colon, rectum and kidney has been noted in males [334, 349] Other tumors associated with dermatomyositis have included Hodgkin's disease, multiple myeloma, retroperitoneal sarcoma, carcinoma of the parotid gland, car-

cinoma of the liver, sarcoma of the bone, carcinoma of the cervix, and a chromophobe adenoma of the hypophysis [371] There are several instances of diffuse reticuloendothelial involvement in patients with satisfactory clinical evidence of dermatomyositis [317, 361]

Improvement in the clinical manifestations of dermatomyositis following radical or suppressive therapy of the tumor is of great practical significance Regression of symptoms has been reported in some instances; in others, no demonstrable change in symptoms attributed to dermatomyositis has followed satisfactory management of the malignancy The initial impression gained from reading the literature is that a consistent improvement in symptoms of dermatomyositis is to be expected if suppression or cure of the malignancy is possible [320] Upon more extensive perusal of the literature this view appears to be a wish or a half-truth only The authors have not enjoyed the fortunate experience of witnessing a cure of dermatomyositis following eradication of a tumor A majority of the patients reported in the literature died before the preparation of the several communications Several cases have been described of the post-morten examination revealing no evidence of metastases or recurrence of the original successfully treated tumor. The patient, nevertheless, died, sometimes following a much shorter clinical course of dermatomyositis than the mean [345]

ETIOLOGY AND PATHOGENESIS

The etiology of this morbid condition is not known Bacterial, parasitic, and viral infections [44, 57] have been implicated in an attempt to explain the pathogenesis of the pathologic findings Organisms that have been singled out include streptococci and staphlococci, with the former in predominance O'Leary and Waisman [354] in 1940 stated "There appears to be little doubt that dermatomyositis is directly or indirectly of infective origin Whether bacteria affect the muscles directly by dissemination by way of the blood stream or by means of toxic products which they

elaborate must remain an open question." There has been little evidence to support this assumption in the intervening period Consistent with this hypothesis, Holmes [332] observed the onset of generalized myositis in a 15-year-old boy one week after an episode of acute pharyngitis. It should be noted that the symptoms at the onset of dermatomyositis may be concentrated on and about the face. This may simulate an acute pharyngitis or influenza and lead to the false premise that an acute infection ushered in the disseminated dyscrasia Wedgewood and associates [378] determined the antistreptolysin titer of the serum in seven patients during the acute phase of the malady, with no elevation noted in any instance It is not difficult in the perusal of several case histories of dermatomyositis to assume that some bacterial infection had appeared early in the course of the disease. No single organism, however, with a latent period between infestation and onset of generalized symptoms is generally recognized in the pathogenesis of dermatomyositis, as is the case in acute rheumatic fever.

A hypersensitivity to toxins, drugs, especially the sulfonamide compounds, and penicillin, sunlight, and other agents has been proposed with less evidence than in some of the other collagen disorders. Photosensitivity appeared to be the inciting agent in two cases reported by Turner [373]. Wedgewood [378] observed exacerbations of acute dermatomyositis concurrently with manifestations of drug sensitivity to sulfadiazine or to penicillin. Until further evidence is available, it is believed that the etiology of this malady must be assumed to be unknown.

PATHOLOGY

The skeletal muscles grossly appear pale and edematous, with the muscle bundles separated by edema fluid Pink or grayish yellow patches of morbid tissue may be observed in otherwise normal muscle structure O'Leary and Waisman [354] stated that the initial pathologic reaction appears within the muscle bundle There is degeneration of the mus-

cle fibrils (PLATE X, page 5) with fragmentation, loss of striations, separation of the myofibrils with edema, infiltration with lymphocytes and enlarged mononuclear cells Coagulation or hyalinization of the sarcoplasm appears in some instances. There may be a significant increase in the number of nuclei of the muscle fibers, with formation of giant cells in the muscle bundles, and an increase of fibrosis of the areolar tissue normally present. There may be little inflammation between the muscle bundles Extensive invasion by lymphocytes, plasma cells and histiocytes [317] around the arterioles may be observed in some areas The vessels may show eosinophilia, thickening of the intima, narrowing of the lumen and, occasionally, thrombus formation [357]. The characteristic necrotic vascular changes of polyarteritis usually are not evident, but the appearance of vessels in thrombotic thrombocytopenic purpura [illegible]
The [illegible]
th[illegible] ...isher [357]
T[illegible] ...inal in the sites of predilection for hypertensive arteriolar changes, i e, kidney, spleen and pancreas. The changes in the vessels in dermatomyositis, according to these investigators, are not specific for this malady

Significant microscopic changes may not be present in muscle obtained by biopsy in the early stages of the disease Hence, the confirmation of the clinical diagnosis from biopsy specimens is not always forthcoming if symptoms have been present for a relatively short period of time. Pathologic changes with widespread destruction are apparent if muscle tissue is examined after the process has been present for several months Evidence of acute as well as of chronic changes may be observed side by side [349] The diaphragm, pharyngeal and ocular muscles in some cases show changes similar to those of the skeletal musculature

Microscopic examination of involved skin (PLATE XI, page 6) reveals findings that may be indistinguishable in selected instances from those in patients with scleroderma There is thinning of each of the layers with dystrophic

keratosis, moderate follicular plugging and alteration of the collagen tissue [*341*]. The bundles lose their fine fibrillary structure, become thickened and tend to accumulate in irregular columns. The papillary bodies become atrophic, and the epidermis appears as a smooth, even layer. The germinal cells show a tendency to degeneration, as reflected by the cytoplasm of vacuolated areas. The nuclei assume a granular and a disintegrated appearance Hair follicles and sebaceous glands show evidence of degeneration There is perivascular cellular infiltration of lymphocytes, plasma cells, histiocytes, fibroblasts and mast cells [*367*] Precapillary arterioles and venules may show thickening of their walls. This is particularly apparent in the intima Collagen deposits, localized areas of necrosis, cellular infiltration and increased vascularity extend into the subcutaneous spaces. Whether the subcutaneous tissue is affected by direct extension of the process in the skin peripherally, or the muscles centrally, has not been determined Possibly the affliction extends from each area Microscopic changes in subcutaneous fat include edema, mucoid degeneration, normal cell infiltration, fibrous tissue replacement and calcification. The subepicardial and periadrenal fat shares in the disseminated process

The heart muscle may show swelling, and early pyknosis of the nuclei of individual fibers Microscopic changes similar to those seen in the skeletal muscle have been noted. Interstitial edema, focal inflammation and mucoid degeneration of the interstitial connective tissue in the myocardium, and fibrosis of the endocardial connective tissue may be present [*377*] In isolated instances, nonbacterial endocarditis and pericarditis have been observed.

Lesions of the intestinal tract have been demonstrated in a number of patients with dermatomyositis Ulcers of the esophagus, stomach, portions of the small bowel and rectum have been described [*336, 318, 377*]. The ulcerations have been associated with edema and cellular infiltration of the walls of arteries and veins [*24*] Subsequent stages of this process lead to mucoid and fibrous thickening of the intima.

with narrowing of the lumen and thrombosis Examination of the liver may show perilobular infiltration with large cells and clear cytoplasm Examination of the spleen may show congestion and infarction

The kidney is particularly susceptible to extensive vascular changes One patient with dermatomyositis seen early in the course of her disease [*372*], developed generalized calcinosis with skin changes that suggested scleroderma Pathologic examination of the kidneys showed endarteritis of the interlobular arteries The medullary branches of the renal and arcuate arteries were normal Sections of the affected arteries revealed infiltration of the subintimal substance by a pale basophilic mucinous material. Stains for elastic tissue revealed limitation of the lesion to the intima The internal elastic lamina was intact in most areas, the lumina markedly narrowed The lining endothelial cells were swollen and basophilic but showed no actual proliferation Some vessels were occluded by hemorrhagic thrombi with fibrinoid necrosis limited to the intima and the inner half of the muscularis Because of the unusual vascular changes, Keil [*80*] believed their relation to dermatomyositis should be questioned until other examples were discovered Wedgewood [*378*] considered that the vascular lesions in dermatomyositis were difficult to distinguish from those of thrombotic thrombocytopenic purpura but were unlike those of polyarteritis in that necrosis and inflammation of the vessel wall was minimal or absent

CLINICAL FINDINGS

The disease may begin insidiously with a low-grade fever, malaise, minimal aches and pains of the extremities, and without any significant preceding medical event The onset was sudden in only 24 per cent of the cases reported by Sheard [*363*] Thirty-two per cent complained of edema or a rash on the face as the presenting symptom A majority of the others noted muscle aching, muscle weakness or fatigue

Some patients may suffer an acute viral or bacterial infection at the onset of the malady, as noted above. Pharyngitis, tonsillitis, sinusitis, an acute middle ear, measles or influenza appear to be casually related Parturition preceded symptoms in cases reported by Grayzal and Lederer [326], O'Leary and Waisman, Pagel and associates [357], as well as in a case reported by us [372]. Edema of the face, particularly in the periorbital region, is usually admitted [317, 369]. This may be present for only a few days. Cutaneous manifestations in some patients precede symptoms indicative of muscle involvement An erythematous eruption of the characteristic butterfly distribution may suggest SLE, or the rash may be confined to the extremities Vasomotor phenomena sometimes are noted initially.

The cutaneous manifestations are present at some stage of the disease in most instances and are independent of muscle involvement as determined by symptoms or clinical examination Erythema may be present with or without subcutaneous edema and may be mottled or diffuse, livid or rosy The term "heliotrope" has been applied to the appearance of affected eyelids. The face and the V of the neck are the common sites of erythema. These are followed in frequency by involvement of the extensor surfaces of the arms, the legs and the trunk [327]. When edema is present, it may be pitting or brawny and indurated Purpura, vesicles and bullous formation have been reported. Ulceration of the buccal mucosa or of the esophagus has been observed [369].

During the natural course of the disease, the cutaneous manifestations undergo alteration Pigmentation, atrophy and telangiectasia may predominate at a later stage These changes may be sharply demarcated from normal skin on the exposed portions of the body. The similarity to the dermatitis of pellagra, the pigmentation of adrenal insufficiency, or localized morphea may confuse the presumptive clinical diagnosis Wedgewood [378] noted erythematous, atrophic and scaly lesions in children with a network of fine blood vessels visible over the extensor surfaces of the joints, par-

ticularly the knuckles, elbows and knees Partial alopecia has been reported in several patients with dermatomyositis [*40, 342*]. Reich and Reinhart [*359*] observed a nine-year-old boy with marked hypertrichosis of the knees, elbows and temporal regions. Thickened, tight, glossy and inelastic skin highly suggestive of scleroderma appears in some patients There may be subcutaneous calcification and extrusion of calcium deposits through the skin, if the malady has been present for a period of time [*321, 326, 366, 378*]

Muscular weakness may be prominent, or it may be a relatively insignificant clinical feature [*315*] Any striated muscle may be affected, although there is a tendency for the development of bilaterally symmetric lesions The large muscle masses are more likely to be involved than the pharyngeal, laryngeal, intercostal, diaphragmatic or ocular groups The patient may be unable to wash his face or comb his hair if the shoulder muscles are afflicted The proximal muscle groups of the upper and lower extremities are more likely to be involved than the distal groups

A majority of patients have diffuse muscle tenderness, others deny this symptom The dissociation between subjective and objective evidence of muscle involvement has been mentioned time and again in the literature Extensive involvement upon microscopic examination has been discovered in muscles that have been neither painful in repose nor tender on palpation The consistency of involved muscles may appear normal, or they may feel doughy, firm and fibrous The patient may walk with an unsteady gait and a shuffle because of weakness of skeletal muscles. Falling while walking has been reported [*359*] The patient may be unable to sit up in bed or even hold up his head with disseminated muscular involvement Weakness of the facial and glossal muscles makes eating and speaking difficult. Extensive involvement of muscles of respiration and deglutition may be directly related to a fatal termination [*378*] Weakness of the sphincters of the rectum and bladder has been observed [*352*] Muscle atrophy may be apparent, and extensive

fibrosis with contractures of elbows, knees, hips and fingers develop if the disease progresses into the subacute or chronic phase.

Lisman [346] has described in detail the ocular changes in one patient with dermatomyositis and compared his findings with a similar case reported by Bruce [313] The patient, a 53-year-old male, had suffered generalized weakness for approximately six months The eyelids were swollen, and the surrounding skin was pink from telangiectasia The edematous area of infiltration pitted upon pressure The lower lids hung in folds and were tender to touch This was attributed to involvement of the orbicularis oculi Postmortem examination showed hyaline and lipid changes in the external plexiform layer of the eye, especially around the macula, and a few scattered hemorrhages in the retina The vessels showed no pathologic changes. Paralysis of the extraocular muscles has been reported but diplopia rarely so Ptosis, strabismus, iritis, nystagmus and exophthalmos have been recorded Retinal hemorrhages and exudates may resemble the cotton-wool fluffs of albuminuric retinitis [319, 351] The communication by Bruce [313] in 1938 contains an excellent bibliography of the eye findings in dermatomyositis

The upper respiratory passages, the bronchi and the lungs may be involved, with dyspnea, hoarseness or an alteration in the pitch of the voice Involvement of the intercostal muscles may contribute to the decreased efficiency of the lungs as measured by a diminution in vital capacity. Pleural effusion has been reported Symptoms of cardiac dysfunction, dyspnea, cyanosis and edema may be observed, although involvement of the myocardium or endocardium is infrequent. Tachycardia and palpitation are assumed to be caused by the generalized process and not because of specific cardiac involvement Pericardial effusion associated with cardiac failure has been reported [80]. The blood pressure may be in the low normal range; it has been elevated in a few patients There is no direct correlation between urine findings and an alteration in blood pressure.

Involvement of the gastrointestinal tract may produce symptoms that are indistinguishable from those of systemic scleroderma They include stomatitis, myositis of the tongue, dysphagia [344] and epigastric distress Occasionally the liver is enlarged Splenomegaly and lymphadenopathy indicate involvement of the hematopoietic system These are uncommon clinical observations

The central as well as the peripheral nervous system may be affected [343] Mental confusion, psychosis and delirium have been reported Deep tendon reflexes may be depressed or absent Hyperesthesia, numbness of the hands and feet, and foot drop have been responsible for the designation "neurodermatomyositis"

The association of dermatomyositis with myasthenia gravis or with thyrotoxic myopathy has been discussed by *Ragan [358] and Dowling [322] The muscle weakness in* myasthenia gravis or severe thyrotoxicosis bears a casual similarity to that of dermatomyositis Microscopic examination of affected muscles also reveals selected pathologic changes common to each malady Creatinuria [328, 378] and osteoporosis have been observed in dermatomyositis as well as in thyrotoxic myopathy Since either finding may be explained upon recognized facts, one is not justified in concluding that the diseases are intimately related

LABORATORY FINDINGS

The routine laboratory studies may show a mild anemia and a slight elevation in the white blood cell count with a relative lymphopenia. Eosinophil percentages usually are within the normal range, but may be as high as 25 per cent [363] The erythrocyte sedimentation rate may be elevated out of proportion to the constitutional symptoms, as is observed in the other maladies under discussion The Wassermann reaction is negative No biologic false-positive reactions have been reported The LE cell test is negative [347] Serum protein concentration may be reduced with little or no change

in the albumin-globulin ratio. A slight increase in the concentration of gamma globulin has been observed. This item may be helpful in excluding SLE, a malady with a significant elevation in this fraction. There is no characteristic alteration in the serum concentration of sodium, potassium, chloride, bicarbonate, calcium, phosphorus or alkaline phosphatase in



FIG 11 —Roentgenogram of the chest of a patient with acute dermatomyositis There is extensive interstitial infiltration This patient had considerable dysphagia but no recognized episode of acute pneumonitis

either the acute or the later stages of dermatomyositis An albuminuria may be expected during periods of activity of the disease. Red blood cells will be found in the urine occasionally [80] Porphyrin excretion has been studied with normal values [354]. In several instances, cerebrospinal fluid has been reported within normal limits. The electrocardiogram may show changes suggestive of interstitial fibrosis of the myocardium The alterations consist of prolongation of

the P-R, QRS and Q-T intervals, minimal variations in the appearance of RS-T segments and T waves, as well as slurring and notching of QRS deflections in multiple leads

Fluoroscopic examination of the chest may show diminished expansion of the lungs and reduced excursion of the

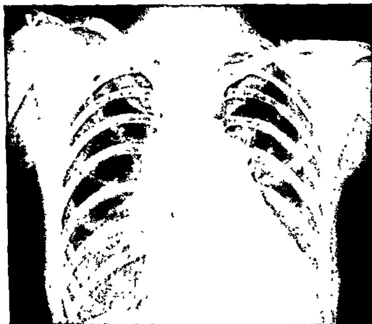


FIG 12—Roentgenogram of the chest of a patient with acute *dermatomyositis There is marked enlargement of the heart shadow* The lung fields show a diffuse increase in interstitial density There are calcified lesions and apical thickening

diaphragm X-ray study may reveal interstitial infiltration (FIG 11) or diffuse fibrosis (FIG 12) Examination of the soft tissues in chronic cases may reveal extensive subcutaneous calcification and osteoporosis (FIG 13) Calcium deposits occur along fascial planes such as in the axillae and the plantar surfaces of the feet as well as in subcutaneous areas along the extensor surfaces of the forearms and in the

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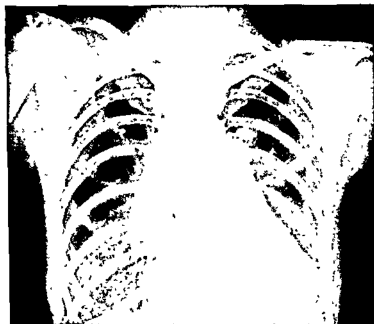


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subcutaneous spaces of the fingers, toes and buttocks
incidence of involvement of the intestinal tract upon r
genographic examination is considerably less than is
served in systemic scleroderma. The changes when pre
however, may be indistinguishable. Narrowing of the lu
gross segmentation, loss of mucosal pattern and dela



FIG 13—Roentgenogram of the pelvis of a patient with der
tomyositis and calcinosis Profound muscle weakness and facial ed
appeared three years before Extensive calcium deposits have de
oped in the buttocks

transit are characteristic features (FIG 14) Reference sho
be made to additional discussion of these findings in
following chapter, SYSTEMIC SCLERODERMA

DIAGNOSIS

The disease may be suspected in patients with atypi
rheumatoid arthritis or with acute rheumatic fever who
not respond to current therapy. Muscle weakness or tend

ness, particularly of the shoulder girdle and upper arms, together with skin lesions, fever and malaise, should suggest the possibility of acute dermatomyositis Inquiry should be made regarding a previous history of Raynaud's syndrome or of presenting complaints of facial or periorbital edema Patho-



FIG 14—Roentgenogram of the esophagus taken several minutes after a swallow of barium in a patient with acute dermatomyositis The lower midportion is dilated The barium passed into the stomach slowly

logic changes in muscle and skin from biopsied material are most helpful in the mild or early case A negative biopsy in a patient with clinical evidence of dermatomyositis does not exclude the diagnosis A second or even a third biopsy may reveal the diagnosis, if the clinical possibility persists The optional sites for muscle biopsy are the pectoralis major and

the deltoid group A portion of altered skin over a mass of tender muscles should be taken if changes are present concomitantly. Pathologic findings have been observed in both muscle and skin that did not suggest involvement clinically. Madden [347] has reported the observations in 12 muscle biopsies from eight patients who were suspected, from clinical findings, of having dermatomyositis. Degenerative changes were present in all except one patient The severity of the myositis was a function of the clinical severity of the malady. Differentiation from the muscle changes in SLE was included in the discussion Myositis and degeneration were detected in six out of 19 patients with SLE. These changes were minimal except in one patient who had "rheumatic fever" also.

The differential diagnosis of dermatomyositis includes the several diseases as noted above as well as Stevens-Johnson syndrome, systemic scleredema, trichinosis, sarcoidosis, thyrotoxic myopathy, progressive muscular dystrophy, amyotrophic lateral sclerosis, infantile paralysis, myasthenia gravis and Addison's disease.

CLINICAL COURSE

The disease is believed to be fatal in most instances. The clinical course may be undulating but usually becomes progressively worse. More than 50 per cent of the patients with the acute fulminating type die without a demonstrable remission intervening Death within eight weeks from onset of symptoms has been reported [365] The average expectancy under current therapy in patients without a malignant tumor is approximately three years from onset of clinical symptoms Survival may be prolonged for a decade or more if the disease becomes partially quiescent and regresses into the subacute or chronic stage. Remissions with apparent restoration of health have been observed to occur spontaneously [310, 330, 354, 378], induced by steroid therapy [49, 355], or by other pharmacologic agents [381], and following removal of a malignant tumor Death from intercurrent infection, car-

diac failure, respiratory insufficiency or renal insufficiency may be expected in the acute fulminating type Malnutrition and invalidism from extensive contractures in the chronic phase may contribute to similar terminal events.

In our series of more than a score of adults, evidence recently brought up to date shows only two patients alive and in remission One, a 51-year-old female, has experienced a remission for more than eighteen months that is believed to be associated with adrenal hormone therapy. The second patie [illegible]
two [illegible]
no s [illegible]
last report Each of the other patients either is dead, shows manifestations of active dermatomyositis, or is handicapped by chronic changes The cause of death before the antibiotic era was attributed frequently to an overwhelming infection Overwhelming infection is apt to be a serious problem at the present time, if there is weakness or paralysis of the pharyngeal and intercostal muscles which permits aspiration of products of digestion and the development of pneumonia [illegible]
factors in the chronic stage of dermatomyositis associated with calcinosis

TREATMENT

Numerous drugs have been recommended in treatment, but no conclusive evidence has been presented attesting to the obvious benefit of a single item or a combination in a series of patients with acute dermatomyositis The vitamins individually and collectively have been disappointing The same may be said for the antibiotics, which have included penicillin, streptomycin and aureomycin Testosterone was held out as a hopeful drug several years ago [*339*] Because this preparation tends to decrease creatine excretion, it was assumed that this effect would help restore muscle anabolism

Temporary improvement followed administration of this drug, but lasting benefits have not been observed. Similarly, para-aminobenzoic acid [381] has been found to be helpful to some patients These results have not been confirmed generally. Cortisone [342], hydrocortisone, prednisone and ACTH [358] are of some value, even though the effect is symptomatic and not curative The antipyretic, appetite-stimulating and malaise-inhibiting effects of the adrenal hormone are not to be disregarded. The authors believe that unless there is a specific contraindication, the adrenal steroids should be administered up to a point of producing the full pharmacodynamic action as manifested by one or more of the recognized features of Cushing's syndrome A minimum clinical trial of two or three months should be given to each patient *These preparations should be continued indefinitely if improvement is observed.* Each of the patients that we are following regularly is maintained on one of the active agents

A tendency to the development of contractures should be combatted with physiotherapy, traction, casts, splints and corrective operative procedures. Correct positioning in the early stages of the malady may be helpful in order to prevent deformity, as may a balanced program of rest and activity Respiratory distress may be mitigated with oxygen therapy or a mechanical respirator. If a malignant tumor is present, this should be treated as effectively as possible. Opiates should not be withheld if muscle pain is severe and the disease is *progressing*

Systemic Scleroderma

SYSTEMIC SCLERODERMA in the late and well developed stage may be recognized more readily upon clinical examination than any of the other maladies described in this monograph Although multiple systems of the body are involved in the disseminated process, cutaneous manifestations are commanding and usually supply the clue to the diagnosis (PLATES XII–XIII, pages 6–7) The internal pathologic alterations embrace the gastrointestinal, cardiorespiratory, musculoskeletal and genitourinary systems, respectively. The essential microscopic lesions consist of degenerative and sclerotic changes in the connective tissue throughout the body with obliterative lesions in the arterioles The disease is prone to relapses and remissions, but ultimately pursues an unrelenting deteriorating course Death may occur within a period of a few months in patients who are affected by a rapidly fulminating type The average duration of life after onset of symptoms, however, is much longer The disease may persevere for a decade or longer before one or more complications prove fatal Disabling skin, muscle and joint changes are evident as well as diffuse subcutaneous calcinosis in the uncompromising chronic cases

The relationship between circumscribed scleroderma, or morphea, Raynaud's syndrome and systemic scleroderma, respectively, has not been determined [*408*] Systemic scleroderma probably should be considered as quite distinct from the two relatively benign maladies Circumscribed scleroderma and Raynaud's syndrome may be recognized clinically, and usually persist as distinct and separate entities A transition from circumscribed scleroderma to systemic sclero-

derma or from uncomplicated Raynaud's syndrome to systemic scleroderma is not a unique observation These phenomena more than others have been responsible for the belief in the intimate relationship of the several maladies. An explanation equally acceptable to the authors and to others is that the tissue response of the body is limited, while the number of inciting agents may be legion. The relationship between systemic scleroderma and acute dermatomyositis, likewise, is noteworthy [*445*]. Several competent physicians have stated that dermatomyositis and scleroderma should be considered as one disease We believe that they are distinct clinical entities. In this discussion the distinction between systemic scleroderma and dermatomyositis will be maintained in the hope that a clearer presentation will result

When calcinosis universalis develops in patients with scleroderma, it should be interpreted as a complication, not as a new or unrelated malady. There is no essential clinical difference in the chronic deforming stage of systemic scleroderma with calcinosis, and a similar stage of dermatomyositis. In an analysis of 39 cases of generalized calcinosis in children, 15 years or younger, Rothstein and Welt [*360*] observed that a diagnosis of scleroderma had been made in 40 per cent, and a diagnosis of dermatomyositis in 11 per cent

HISTORICAL

The early descriptions of this malady are credited by Lewin and Heller [*453*] to Zacutus Lusitanus in 1634, to Diemerbroeck in 1660, and to Curzio of Naples in 1752 Gintrac in 1847 is believed to have been the first to use the term scleroderma, according to these authorities Raynaud was familiar with hardening of the skin on the extremities which accompanied the phenomenon he described in 1862, *and which is recognized by the eponymic term* Addison [*383*] described two cases of "keloid" or "scleriasis" in a posthumous collection of his writings published in 1868, instances which surely would be labeled scleroderma now

"At length the part originally affected becomes more or less hide-bound, and a similar change taking place around the more superficial fasciae and tendons, the latter become so tightened, fixed, and rigid, as to be no longer capable of performing their proper functions, and to such an extent, that the whole of a limb, but especially the fingers, may be permanently contracted, bent, and rendered almost as hard and immovable as a piece of wood, thereby impeding progression, distorting the gait, and making the patient a poor miserable cripple for the remainder of his life

"As these changes proceed the cutis manifests a tendency to superficial ulceration or excoriation the whole appearance very closely resembling the remains of an extensive and imperfectly cicatrised burn"

Hutchinson in 1896 called attention to the hardening of the skin on the extremities of a patient which he identified as acroscleroderma [*435*] Symptoms which began as vasospasm had been present for nearly a decade A few years earlier, Weber attributed subcutaneous deposits of calcium in patients with scleroderma to a form of gout [*502*] Thibierge and Weissenbach [*500*] rediscovered the clinical entity of calcinosis with scleroderma in 1910 The eponymic term, Thibierger-Weissenbach syndrome, is employed sometimes to identify this late manifestation of the malady In 1938, Atkinson and Weber [*385*] prepared an excellent historical summary of the subject of calcinosis Finlay [*421*] observed significant limitation of pulmonary expansion in a male patient with scleroderma in 1891, and is credited with the recognition of the association of scleroderma and pulmonary fibrosis The esophageal disturbance of scleroderma was reported first by Ehrmann [*418*] in 1903 Rake [*483*] reported pathologic findings in the small bowel in 1931 Masugi and Ya-Shu [*465*] observed fibrinoid changes in the blood vessels of a case of scleroderma in 1938 and suggested that an allergic reaction was responsible for the structural alterations In recent years Goetz [*427*] proposed the term, "progressive systemic sclerosis," in place of generalized

scleroderma. Dowling [*414*], who believes that scleroderma and dermatomyositis are manifestations of essentially the same disturbance, has proposed the term, "myopathic scleroderma " This proposal has not received general acceptance

INCIDENCE

Systemic scleroderma is not a rare malady The increased appreciation of the potential incidence of the disease is largely responsible for the diagnosis being suspected more often now than formerly. In 1928, Longcope [*459*] commented upon "the unusual opportunity of observing eight cases of generalized scleroderma at the Johns Hopkins Hospital in recent years." Twenty-five years later, Beigleman and associates [*394*] described 15 cases seen in Boston over a period of two years only; Evans and associates [*420*] reported one series of 38 cases, while Boyd and associates [*400*] described roentgen findings in 63 patients of scleroderma observed at the Duke University Hospital during a span of two decades. Alexander [*424*] noted that approximately one patient with scleroderma was admitted to Barnes Hospital each year over a twenty-year period prior to 1950 During the first nine months of 1952, eleven patients with scleroderma were admitted

The highest incidence of affliction is in the fourth and fifth decades of life, although several instances have been reported in children One of the youngest patients described in the literature was an infant girl [*448*] Shortly after birth her skin was noted to be tense and hard A clinical diagnosis of scleroderma was made at that time She was still alive when her case was reported again at the age of eighteen months Diffuse calcinosis with scleroderma has been observed in one child nine years old [*470*]. At the other end of the life span, patients in the seventh decade have been afflicted [*450*, *490*] Females tend to be more susceptible; the ratio ranges from 3.1 to 2·1 [*394*, *420*, *488*]. There are no reported examples of the malady appearing two or more

times in one family [450]. Several cases of systemic scleroderma in Negroes have been observed [400, 450] The review of Matsui [466] includes six cases among the yellow race

RELATION TO OTHER COLLAGEN DISORDERS

A suspicion of rheumatoid arthritis [481, 503] has been entertained in some patients with scleroderma in the early months after onset of symptoms The incidence of arthralgia or symptoms suggestive of rheumatoid arthritis is considerably lower than in patients with SLE or acute dermatomyositis Marked limitation of motion or ankylosis of the joints of the fingers, as is observed in some patients in the late stages of the malady, is believed to be a result of the generalized sclerodermatous process, even though rheumatoid arthritis may be simulated The initial complaints in scleroderma may comprise intolerance to cold, paresthesias, and stiffness sufficient to suggest Raynaud's syndrome. Caughey and Richardson [406] studied one female with a history of symptoms of vasospasm for ten years before evidence of scleroderma appeared She died nine years later. No instances of scleroderma mimicking acute rheumatic fever, followed within a short time by clinical findings of scleroderma, were discovered in the literature

Some of the findings believed typical of acute dermatomoysitis may be observed in systemic scleroderma [455] Edema of the face and of the periorbital region with muscle pain and weakness usually exclude scleroderma One patient, however, described by Beigelman and associates [394], with facial swelling highly suggestive of dermatomyositis, developed systemic scleroderma within one year Dowling and Griffith [322] stressed the profound muscle weakness that may appear in either malady Seville [492] reported a 56-year-old male with the presenting symptoms of a rash over the forearms and edema of the eyelids such as may be noted sometimes in patients with dermatomyositis Three months later the skin of the arms, hands and face became

taut This was followed by weakness of the legs, shoulders and elbows. Biopsy specimens of the skin and muscle showed changes suggestive of dermatomyositis as well as of scleroderma Scleroderma appeared to be the likely clinical diagnosis Note also should be taken of the case reported by Kampmeier [*441*] with pathologic evidence of scleroderma, dermatomyositis and SLE

A similarity to SLE has been noted because of the cutaneous manifestations and selected pathologic findings [*357*] Another patient reported by Beigelman and associates [*394*] experienced fever, anemia and an erythema that suggested SLE The esophageal lesions and low-grade chronic course were characteristic of scleroderma Vehemently opposed to an intimate relationship of these similar maladies are Baehr and Pollack [*387*], who stated that· "Disseminated lupus erythematosus and diffuse scleroderma have in common a similar morphologic expression, namely, fibrinoid degeneration of collagen and identical lesions of blood vessels, glomeruli, endocardium, and the serous and synovial membranes However, they are so dissimilar clinically that they seem related neither to each other nor to rheumatic fever, rheumatoid arthritis, serum sickness, periarteritis, or thromboangiitis obliterans, in which similar collagen changes may occur as part of the pathologic process "

ETIOLOGY AND PATHOGENESIS

The cause of the disease is unknown, and there is no generally accepted theory regarding the development of symptoms Hypersensitivity has been considered, as in the other maladies presented in this monograph, but has been discarded because of the lack of evidence. The onset of typical skin changes may be preceded by an acute infection, although no one bacteriologic agent has been implicated [*411*] Boardman [*398*] reviewed the literature in this regard and noted that the following infections either preceded its onset or appeared in association with scleroderma· typhoid fever, bronchopneumonia, lobar pneumonia, pulmonary tu-

berculosis, bacteremia, scarlet fever, measles, malaria, tonsil-
... and syphilis Boyd [400] observed severe sinusitis in
e out of six patients with scleroderma Repeated felons, a
or tenosynovitis and osteomyelitis were accorded etiologic
nificance in one patient studied by Beigelman and associ-
s [394]

The central nervous system as well as the peripheral
ervous system has been implicated in the pathogenesis of
ystemic scleroderma Complete [467] or partial hemi-
atrophy [475] of the face associated with a central nervous
system lesion has been noted Ormea [477] demonstrated
degenerative changes in ganglia and fibers of the sympa-
thetic nerves of the skin, and presumed that these changes
preceded any abnormalities of the collagen tissue He con-
luded that scleroderma was primarily a disease of the au-
tonomic nervous system and that alterations in the collagen
were secondary The symmetric distribution of cutaneous le-
sions and the symptoms of Raynaud's syndrome initially
suggest a vasomotor pathogenesis with sympathetic nervous
system dysfunction The symptomatic relief reported in some
patients following surgical sympathectomy may be offered
as additional evidence in support of this hypothesis The in-
frequent resort to sympathectomy now suggests that it did
not produce the beneficial results hoped for, and that the dis-
ease is not primarily a result of sympathetic nervous system
imbalance

Emotional tension and anxiety have been postulated as
pathogenic agents There is slightly more clinical evidence
in support of the emotional factors in patients with sclero-
derma than there is in any of the other unusual collagen
disorders Baehr [4] discussed the emotional factors in pro-
ducing angiospasm, an integral feature of Raynaud's syn-
drome Mufson [172], as well as McMahon and associates
[168], has presumed a direct correlation between aggrava-
tion of symptoms in scleroderma and emotional stress. Note
may also be made of the intimate relationship in some pa-
tients between emotional factors and exacerbations of joint

symptoms in rheumatoid arthritis *without demonstrative etiologic relationship.*

Strong evidence supports the probability that vascular changes in the digits [*411, 426*] are responsible for the sclerodermatous lesions in these parts, i.e., sclerodactylia. Brown and O'Leary [*403*] detected changes in the capillaries of the nailbeds in patients with scleroderma that were similar to those in patients with Raynaud's syndrome. The capillaries were markedly reduced in number, apparently a function of *the severity of scleroderma The diameters of the loops were* increased to such an extent in some instances as to obliterate the spaces between the arterial and venous limbs The temperature of sclerodermatous fingers tended to remain below room temperature [*404*] Lewis and Landis [*456*] showed that the structural alterations in the small peripheral arteries in Raynaud's syndrome were independent of the presence or absence of scleroderma They concluded that in local or systemic scleroderma as well as in Raynaud's syndrome, the *disturbance resides in the vessels Prinzmetal* [*481*] confirmed these observations and extended them to include evaluation of the constriction produced by the atrophic skin Sclerodactylia was presumed to be the result of a combination of vascular insufficiency and constriction of the skin Sympathectomy was followed by an increase in temperature of the fingers of patients who served as controls There was little or no rise in temperature in the patients with scleroderma. The nonelastic skin prevented vasodilatation after *sympathetic tone had been abolished*

There is little substantial evidence that a dysfunction of one of the endocrine glands is responsible [*405*]. Thyrotoxicosis and Addison's disease are similar in several aspects to systemic scleroderma and have been allied with scleroderma in selected instances Weight loss, muscle weakness and cutaneous pigmentation may be present in each malady. Longcope [*459*] discussed this association in eight cases with scleroderma. Dowling [*415*], reviewing 19 cases of scleroderma from the literature, with two from his clinical prac-

tice in which the thyroid was examined histologically, observed pathologic alterations in the gland without exception. He noted also that creatinuria developed in thyrotoxicosis and in scleroderma. Osler reported the failure of thyroid extract to improve the clinical abnormalities in eight patients with scleroderma. In discussing the similarity between adrenal insufficiency and scleroderma, Longcope reported a case of acute systemic scleroderma in a young male. Post-mortem examination disclosed atrophy of one suprarenal gland and interstitial orchitis. Leinwand [450] observed foci of degeneration of the adrenal glands in one case.

There is some justification for implicating the parathyroids in the etiology. In the chronic or subacute case of scleroderma, the calcinosis upon casual inspection may be similar to that seen in hyperparathyroidism. However, when the concentrations of calcium, phosphorus and phosphatase have been determined in the serum of patients with scleroderma, significant variations from the normal have not been observed. Nor was Leriche able to demonstrate consistent benefit in sclerodermatous patients following parathyroidectomy [451]. Bernheim and Garlock [395] have postulated that an inadequate intake of calcium initiates the pathologic changes. Since calcium affects the permeability of the cell, vasospasm and Raynaud's syndrome were assumed to follow an inadequate calcium intake. This theory of pathogenesis has not been accepted generally. Brody and Bellin [401] presumed that impaired circulation and necrobiosis preceded calcium deposition in the soft tissues. Bauer and associates [390] attributed the vascular changes to calcification and considered neither inflammatory changes nor vascular changes to be causative factors. Brooks [402], in an excellent review of calcinosis, concluded that local fibrous tissue damage precedes calcium deposition. If this view is correct, one would not expect an alteration of the serum calcium and phosphorus concentration in the blood to be responsible for the precipitation of calcium in soft tissues.

Malignant tumors do not have the intimate association

noted in acute dermatomyositis Barlow [388] reported an adrenal adenoma in a patient with scleroderma. Stiffness of the joints had been present for more than two years Death was attributed to cardiac failure, not primarily to the adrenal tumor A review of the literature at that time (1939) revealed no other instance of an adrenal tumor associated with scleroderma

PATHOLOGY

Two types of lesions may be identified microscopically in the skin of patients with scleroderma. The first type is the one usually present (PLATE XIV, page 7). The epidermis is thin, the rete pegs are broadened or flattened, the dermis may be extremely avascular and consist of compact, homogeneous, acellular collagen tissue which is present in increased amounts Elastic fibers are decreased and fragmented The collagen tissue in the deeper areas undergoes hyalinization, and in selected instances may show calcium deposition Foci of foam cells may be present in otherwise unchanged fat with varying amounts of amorphous and granular eosinophilic substance. Calcification may appear as deeply basophilic spicules and may be accompanied by numerous monocytes and multinucleated foreign body giant cells This may be more pronounced in the deepest portions of the panniculis overlying involved muscles

Goetz [427] has described a second type of lesion in the skin from the fingers of patients with scleroderma Hyperkeratinization and flattening of the rete pegs are predominant features Collagen degeneration in the dermis with increased vascularity and cellularity may be associated with marked diminution of subcutaneous fat. Blood vessels show some of the characteristic changes of the other collagen disorders, with fibrinoid degeneration and fragmentation of the inner elastic membrane In an investigation of the skin by the electron microscope, Seville [492] noted a great increase in amorphous material.

Considerable variability in skeletal muscle involvement

has been observed in cases reported in the literature Areas
that are sampled post-mortem show different phases of myo-
sitis {449} There may be profound variability in the caliber
of the muscular fasciculi; many show shrinkage with wide
separation from the perimysium (PLATE XV, page 8)
Some muscle bundles are eosinophilic, swollen and lacking
in striations, others are frayed and display separation of the
myofibrillae Isolated muscular strands exhibit marked
nuclear proliferation; others are replaced by fibrous scars
Scattered foci of lymphocytic infiltration distributed peri-
vascularly and within the interstitial tissue have been noted

Gross examination of the esophagus may reveal shorten
ing in length and thickening of the epithelium from the mid-
portion to the cardia {462} Examination of the peritoneal
vity may reveal a slate-grey coloring of the peritoneal
urfaces of the intestine and evidence of an inflammatory
eaction When the bowel is held against a light in selected
nstances of advanced scleroderma, it may appear translucent
because of extensive atrophy {431} Microscopic examina-
tion may reveal atrophy of the mucosa, submucosa and mus-
cularis of the alimentary tract with fibrous replacement from
the esophagus to the sigmoid The muscular layers show
hypertrophy in the earlier stages of the malady, and atrophy
l fibrosis later The vessels in the submucosa may show
llular infiltration, necrosis and thrombosis The lumen may
e obliterated by intimal fibrosis and polymorphonuclear
eukocytes Ulcers and diverticula have been reported in the
esophagus {490}, stomach, duodenum {440} and colon They
are assumed to be the result of edema, intimal fibrosis and
thrombosis of the vessels that supply the wall of the hollow
viscus Unexpected death has been reported in scleroderma
from ulceration of the large bowel, rupture and peritonitis
The myenteric plexus in the esophagus and colon may be
deficient or lacking in ganglion cells The smaller nerve
trunks show myxomatous degeneration and varying degree
of replacement by fibrotic tissue {462} These changes resul
in moderate to severe segmental dilatation and narrowing

the hollow organs Degenerative changes in the liver and infarction of the spleen have been observed.

The lungs share in the extensive pathologic process Post-mortem examination of patients with advanced pulmonary symptoms shows diverse degrees of involvement [*413*, *446*] Getzowa [*425*] has described a cystic sclerosis caused by hyaline fibrotic change in the interstitium of the pulmonary parenchyma. The cysts sometimes are lined by cuboidal epithelium; others show no epithelial lining Obliteration of the capillaries and disseminated fibrosis of the alveolar wall is considered to be an intermediary stage in the formation of cysts Many small alveoli are surrounded by dense zones of fibrous tissue. The alveolar septa are diffusely thickened and infiltrated sporadically with large and small mononuclear cells, plasma cells and a moderate number of polymorphonuclear leukocytes. In other areas the alveoli are dilated and contain fragmented alveolar septa, and in many of the smaller bronchi the muscular coat is replaced by fibrous tissue The bronchioles may be dilated and the walls infiltrated with lymphocytes and plasmocytes. Church and Ellis [*407*] have postulated that some of the cystic changes may represent the late effects of emphysematous bullae which develop because of obstruction and associated chronic infection The arteries and arterioles show thick walls, narrow lumina and sclerosis [*386*, *496*]. The pleura may be thickened and accompanied by unilateral or a bilateral effusion [*397*]

Edema of the epicardium or a pericardial effusion may be apparent upon gross examination of the heart Examination of the myocardium may show scarring extending through the entire thickness of the wall This development led to complete heart block in one patient [*417*]. Microscopically, epicardial fibrosis with flecks of calcified material has been observed [*416*, *428*]. The increase in connective tissue which varies from minimal interstitial fibrosis to extensive hyaline scarring bears little relation to the coronary vascular supply Muscle fibers in uninvolved areas present

a normal appearance The endocardium of the heart and intima of the aorta may be thickened and contain coarse fibrous tissue

The kidneys in scleroderma are particularly susceptibl and show a variegated pattern of normal structure, minima involvement and extensive changes Grossly, the kidney ma have an uneven surface with dimpling and pinpoint hemor rhages [424], and an appearance similar to a shrunken ar teriosclerotic kidney, if the vascular changes are widesprea [466] Microscopically, the medium-sized and smaller ar teries and arterioles are affected [450]. The interlobula arteries show a striking proliferation of loose, acellular cor nective tissue beneath the endothelium [471] Occasionall the vessels are occluded by thrombi in the process of orgar ization Hyalinization of the glomeruli with thickening c Bowman's capsule (the wire-loop feature), cloudy swellin of the convoluted tubules, areas of infarction and pluggin of the tubules with casts have been reported [397] The pro imal convoluted tubules may be filled with colloid casts an show alterations in the epithelium; the remaining tubul appear normal Differentiation from the renal lesions in th other collagen disorders is believed to be possible, accordin to Moore and Sheehan [471] Horn [433] reported calcific tion in the kidney of a patient with the diagnosis of poikil dermatomyositis The clinical description of the case w highly suggestive of systemic scleroderma with generaliz calcinosis Calcium deposits in the kidney have been observ also by Kusunoki [477] The blood vessels throughout th body, particularly the smaller vessels [466], show chang similar to polyarteritis Lewis [455] found that many of th arterioles in a case studied post-mortem showed necrotizin lesions typical of malignant hypertension

The association of Raynaud's phenomenon and scler derma has prompted careful examination of the sympathet nervous system Histologic study of the sympathetic ganglic may reveal sclerosis, chronic inflammation and vascular segmental degeneration with accumulation of lipochrom

granules. In one instance, Richter [*485*] reported mucoid degeneration of the peripheral nerves, associated with tremendous proliferation of connective tissue around and within the nerves throughout the body. It was suggested that the degenerative changes in the walls of the blood vessels supplying the nerves were responsible Cystic degeneration of dorsal nerve roots, sclerotic areas in the brain, the grey matter of the medulla and the anterior horn of the spinal cord, respectively, have been reported Diminution in number and atrophy of the chomophobic cells of the hypophysis with hypertrophy and hyperplasia of the chomophilic cells have been observed [*466*]

CLINICAL FINDINGS

Localized scleroderma, with or without symptoms of Raynaud's syndrome, may be observed as a benign process and may not progress into the diffuse type Systemic scleroderma, the malady under discussion, sometimes is indistinguishable in the early stages from the localized benign form The onset of symptoms in generalized scleroderma frequently is insidious, as in the other collagen diseases, with fever, malaise, arthralgia and vasomotor changes of the extremities [*456*] usually present The hands are more susceptible to vasomotor dysfunction than the feet [*410*] Palmar sweating may be increased or decreased. Intolerance to the cold, together with the color changes suggestive of Raynaud's syndrome [*448*, *488*], is associated with sufficient distress to make a firm impression upon the patient and serves as a specific item of reference. Functional alterations may be present for months or years before irreversible changes in the skin, i e, scleroderma, cause the patient to seek medical advice The face, neck or hands are affected first. Three stages of transformation of the skin may be distinguished clinically [*392*], the first characterized by a diffuse, nonpitting edema, creating a puffy, yellow-white appearance to the skin with flattening of the normal folds. Edema is replaced by fibrosis in the second stage The skin hardens, may be pinched with-

difficulty, and defies separation from the subcutaneous tissues The dorsa of the hands and the feet are prone to develop these manifestations The face begins to show the features that characterize it as a mask Brown pigmentation may appear at this stage, either diffuse or mottled, with areas of depigmentation a common feature [*411*] In the third stage atrophy predominates, the skin over the face becomes firmly adherent to the underlying bony structure and creates a skull-like appearance. Skin folds are obliterated with marked restriction of motion of the lower jaw Skin over the chest may share in the sclerosing process The mucous membranes of the mouth and pharynx may be afflicted with the indurative and atrophic process and associated with shrinkage of the gums, soft palate, uvula and frenulum of the tongue [*460*] Telangiectasia and loss of hair [*475*, *187*] are late manifestations Degenerative and fibrotic changes in the muscles result in weakness and atrophy of the skeletal groups with induration apparent upon palpation Secondary changes in the muscles may also follow profound sclerodermatous changes in the skin Osler [*178*] referred to this stage as "one of the most terrible of all human ills Like Tithonus, to wither slowly,' and like him to be 'beaten down and marred and wasted' until one is literally a mummy, encased in an ever-shrinking, slowly contracting skin of steel. is a fate not pictured in any tragedy, ancient or modern"

The fingers are immobilized in flexion unless measures are taken to prevent deformity Normal use of the hands is impossible They may be extremely atrophic, with palpable calcium deposits on the tips of the fingers This localized phenomenon is associated with absorption of bone and the development of ulcers [*110*] A characteristic feature of the ulcer is a tendency to keep opening and impede healing Areas of gangrene appear, and fingers may be amputated in desperation

Subcutaneous nodules [*491*] and subcutaneous calcification frequently develop if the disease persists for a year or more Diffuse calcinosis associated with scleroderma, in con-

trast to calcinosis of renal rickets or hyperparathyroidism, is identified as the Thibierger-Weissenbach syndrome Atkinson and Weber [385] noted that 32 per cent of 78 patients with calcinosis universalis had scleroderma. The incidence was 40 per cent in 137 cases of calcinosis circumscripta. Any distinction between localized and generalized calcinosis in patients with scleroderma is probably an artificial one, since they represent different stages only of the same morbid process. This view, expressed by Rothstein and Welt [360] in 1936, remains valid Calcium deposits tend to appear in areas subject to pressure, such as the volar surfaces of the terminal phalanges, along the ulnar border of the forearms, the plantar surface of the feet, along the shins, over the patellae, and in the buttocks The overlying skin may be injured; and ulceration ensues if the subcutaneous deposits attain an appreciable size. Calcium salts are extruded in the sludge The hands are more prone to develop ulcers than the feet. Calcinosis may be observed in the axillae and over the trunk In some instances extensive subcutaneous calcification may be demonstrated, with minimal overlying skin changes Visceral calcinosis may appear in the heart and kidneys as noted in the section on PATHOLOGY. Sclerodermatous nodules not associated with calcium deposits have been reported on the upper arms and trunk [491] Microscopic examination reveals the nodules to be composed of degenerated collagen fibrils

Gastrointestinal symptoms, dyspepsia, sour eructations, epigastric distress, anorexia and nausea may appear early in the clinical course in some patients. Involvement of this system may develop in the acute fulminating type of scleroderma as well as in the chronic form. There is poor correlation between the magnitude of cutaneous changes and the severity of gastrointestinal involvement. The tongue may atrophy because of replacement of muscular tissue with fibrous connective tissue. Dysphagia may precede sclerodermatous alteration of the skin [482]. Kaisch [440] reviewed the esophageal findings in six patients with systemic scleroderma Gastrointestinal symptoms appeared within six

months after clinical onset of the malady in one patient. A lapse of more than 20 years occurred in another patient between the onset of cutaneous manifestations and the awareness of gastrointestinal dysfunction. Indigestion and diarrhea developed after an interval of 10 years in one patient described by Aronsen and Wallerstein [*386*]. Abrams, Cannes and Eaton [*382*] presented a detailed history of six patients suffering from scleroderma with gastrointestinal complications. The symptoms of gastrointestinal dysfunction appeared shortly after the onset of manifestations of Raynaud's syndrome in each patient.

Difficulty in swallowing may progress so that the patient is able to swallow liquids only [*412*]. The esophagus no longer will relax following inhalation of amyl nitrite. Involvement of the lower portion of the esophagus may permit regurgitation of acid contents from the stomach, which is conducive to esophagitis, peptic ulceration and fibrosis of the esophageal wall [*382, 457*]. Esophagoscopy will detect ulcers if present, but the procedure may show no evidence of mucosal abnormality in spite of symptoms [*399*]. Biopsy has also failed to reveal diagnostic changes [*482*]. Small bowel involvement may be demonstrated by x-ray in spite of few symptoms pointing to such a process. Sachs and associates [*189*] noted the infrequent appearance of diarrhea in patients with roentgenographic evidence of intestinal involvement. The colon may be dilated, atonic and incapable of proper evacuation. Starvation from inadequate intake and impaired absorption of food is a serious threat in patients with this malady.

Pulmonary symptoms as well as gastrointestinal symptoms have a higher incidence in patients with scleroderma than usually is assumed. A chronic nonproductive cough followed by dyspnea and later severe orthopnea may be noted [*494*]. Spain and Thomas [*196*] have divided the functional changes associated with scleroderma of the lungs into two aspects, the ventilatory and the respiratory disturbances, respectively. The ventilatory function is so impaired, because

of anatomic reasons, that the afflicted is unable to move air in and out of the lungs effectively. The skin and muscles of the thoracic cage restrict normal motion Fibrosis of the diaphragm and pleura with diminution of volume of the lung impedes expansion. There may be diffuse peribronchial fibrosis with obstructive emphysema [*473*]. In addition to the several factors which affect ventilation, impairment of respiratory function may be demonstrated. Thickening of the alveolar walls, narrowing of the lumen, and changes in the blood vessel wall, which may progress to obliteration, impair the exchange of gases across the alveolar membrane This may be demonstrated by a decreased oxygen content of arterial blood following exercise [*422*]. We have observed one patient for more than two years with mild "rheumatoid arthritis." On two occasions, eighteen months apart, a tracheotomy has been performed because of obstruction of her airway. A biopsy specimen of bronchial mucosa taken at the time of the second tracheotomy showed fibrinoid changes consistent with scleroderma. She has improved symptomatically on steroids. There is no evidence from radiographic and fluoroscopic examination of the lungs and gastrointestinal tract of involvement of these structures

Cardiac symptoms usually do not appear in the early stages of the disease; they are late or terminal manifestations. One exception has been reported by Goldman and associates [*428*]. Evidence of cardiac dysfunction appeared initially in this patient. Dyspnea, orthopnea, palpitation, tachycardia and other symptoms of cardiac failure have been observed [*464*, *474*, *503*]. Beigelman and associates [*394*] observed myocardial fibrosis in four out of five autopsied cases. Valvulitis was demonstrated in one and pericarditis in another In the total of 15 patients in the series, 11 had a systolic murmur at some time during the clinical course. Enlargement of the heart was observed in six. Gallop rhythm, pulsus alternans, pericardial friction rub and arrhythmias were also noted In contrast, only three out of

38 cases reported by Evans and associates [420] displayed clinical evidence of cardiac involvement

Deterioration of kidney function complicated by hypertension [419] may be the significant terminal event. Moore and Sheehan [471] reported three cases of kidney involvement in scleroderma and reviewed the literature on this aspect of the disease Each of 11 instances of major renal impairment, collected from the literature, showed an elevation in the concentration of blood urea nitrogen, with the blood pressures either normal or below the malignant range The Lahey Clinic group [420] discovered two examples only of hypertension in a series of 38 patients

Although ocular manifestations are uncommon, retinal exudates and hemorrhages may accompany severe hypertension The association of cataracts and scleroderma (Werner's or Rothmund's syndrome) is a familial disturbance and will not be included in this discussion Jacksonian convulsions are unique in scleroderma Extensive peripheral neuropathy has been observed by Richter [485] in two cases A similarity to the peripheral neuropathy of polyarteritis is exceptional

LABORATORY FINDINGS

Laboratory examination reveals few characteristic alterations in the routine procedures but reflects specific involvement of one or more vital systems The red blood cell count, white blood cell count, and differential count including the eosinophil percentage may be within the range for normals The Wassermann reaction is negative Biologic false-positive tests have not been reported The erythrocyte sedimentation rate may be elevated in the acute phase of the malady Red blood cells, albumin and casts may be present in the urine if there is vascular involvement of the kidneys Retention of nitrogenous products in the blood may be expected as renal insufficiency develops Alteration of the albumin–globulin ratio has been reported [501] In a stud

by Pende [479] of the electrophoretic pattern of the serum proteins in seven cases of generalized scleroderma, the total content showed a decrease with an inversion of the albumin-globulin ratio Hypoglycemia has been attributed to delayed absorption of glucose from the gastrointestinal tract [459]. Abrams and associates [382] reported a flat glucose tolerance curve in two patients [487].

The concentration of serum calcium, phosphorus and phosphatase in patients with or without demonstrable calcium deposits, is within normal limits. Controlled calcium balance studies by Cornbleet and Struck [409] on two patients with scleroderma revealed retention of this element. Large doses of vitamin D resulted in an increased urinary excretion of calcium and phosphorus with little alteration in the excretion of these constituents of the feces. Other investigators have observed a normal exchange of calcium and phosphorus [488] Direct chemical analysis of bone shows normal or decreased calcium content. while the soft tissues show an increased content [447]

Mensuration of the skin temperature of the hands or feet shows a significant decrease below the normal range [456] Capillary microscopy reveals a diminution in the number of capillary loops per field and marked slowing of the blood because of dilatation of the capillaries. Sodeman and Burch [495] measured the distensibility of normal and sclerodermatous skin by a simple procedure They observed that the lack of elasticity in involved skin was a function of the severity of the malady

Roentgenographic changes in the soft tissues in scleroderma with calcinosis may be striking Deposition of calcium appears first in the tips of the fingers (Figs 15, 16, 17); later it may be observed in more proximal areas [437]. The buttocks. shoulders and face may be the site of deposits. Subcutaneous calcification in advanced cases may appear as an armor of fine mesh about the trunk (Figs 18, 19) and in the limbs (Figs 20, 21, 22) coinciding anatomically with the distribution of muscle and fascial planes [469] Radiographic



FIG. 15.—Roentgenogram of the hand of a patient with chronic systemic scleroderma. Symptoms had been present for more than 20 years. There are diffuse calcium deposits.

examination of the fingers shows atrophy and absorption of the terminal phalanges which may progress to complete absorption (FIG. 15). Harper [*431*] suggested that early subcutaneous calcification of the fingers might be overlooked unless lateral films were taken as well as the conventional views. Dense stipling of the terminal phalanges and linear

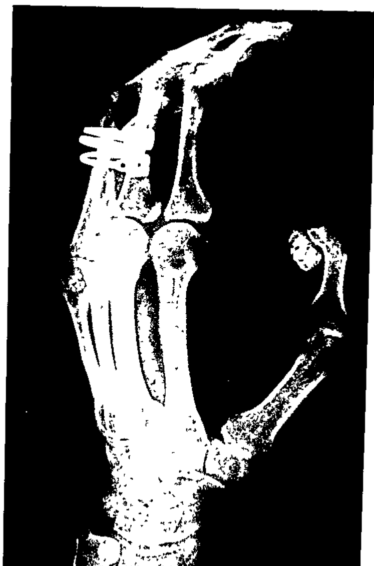


Fig 16—Roentgenogram of the hand of a patient with chronic systemic scleroderma There are calcium deposits in the soft tissues of the fingers and thumb with flexion deformities and decalcification of the digits.



FIG. 17 —Roentgenogram of the hand of a patient with chronic systemic scleroderma There are widespread calcium deposits in the wrist, decalcification of the phalanges and diminution of the joint spaces of the digits



FIG. 18.—Roentgenogram of the axilla of a patient with chronic systemic scleroderma. The calcium deposits are spotty (see FIG. 19).



Fig. 19.—Roentgenogram of the axilla of a patient with chronic systemic scleroderma. The calcium deposits are diffusely distributed in the soft tissues.

streaks of decreased density have been noted [439]. Bársony and Frisch [389] described a band of osteoporosis separating the distal portion from the central portion of the terminal phalanx and synostosis of the mutilated terminal phalanx with the head of the middle phalanx. Robles [487] observed

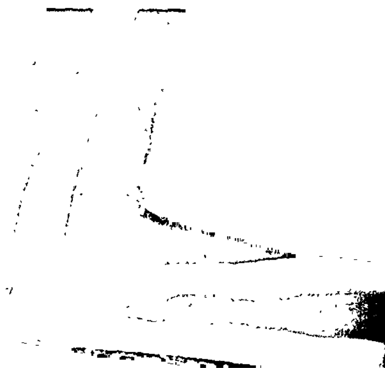


FIG 20—Roentgenogram of the elbow of a patient with chronic systemic scleroderma There are diffuse calcium deposits in the flexor and extensor surfaces

decalcification of the epiphyses adjacent to those joints that showed greatest loss of mobility from sclerodermatous skin changes Localized or widespread osteoporosis with subluxation and dislocation may result from the combined effect of bone absorption and arthropathy Examination by Boyd and associates [400] of the joints of 31 patients with scleroderma

showed changes in 17 that suggested the diagnosis of rheumatoid arthritis (Fig 23) The affected joints included the interphalangeal and carpal joints of the hands, elbows, shoulders, knees, ankles and feet

Radiography of the teeth has disclosed granulomatous foci at the roots [*469*] Widening of the periodontal membrane space which tends to surround the entire root of the tooth at the expense of the alveolar socket has been described. In the earlier stages of the disorder, there may be evidence of

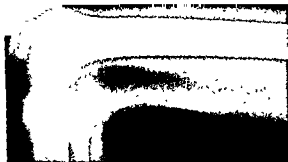


Fig 21 —Roentgenogram of the knee of a patient with chronic systemic scleroderma There is diffuse calcinosis in the soft tissues

resorption of the wall of the alveolar socket, followed by sclerotic changes in the wall The premolars and molars are most often affected [*497*]. The roots assume a slightly tapered shape from absorption of the apices. The involved teeth upon clinical examination may be firm in their sockets [*198*]

The incidence of roentgenographic abnormalities in the gastrointestinal tract is almost as high as in the bony structures but bears little relation to involvement of the skin Roentgenographic studies have included systemic examination of the esophagus, stomach, small bowel and colon Detailed analysis of this subject has been reported by Hale and Schatzki [*129*] in a study of 22 patients, by Boyd and associates [*100*] in 29 patients, and by Harper [*131*] in 14

patients. Several of the patients in the series of Hale and Schatzki were studied by the senior author at the Massachusetts General Hospital. Examination of the esophagus was recommended in seven out of the twenty-two individuals because of symptoms associated with swallowing



FIG 22—Roentgenogram of the foot of a patient with chronic systemic scleroderma There are calcium deposits along the plantar surface

Residual food or fluid was not present at the beginning of the examination in any patient Six of the remaining fifteen admitted some epigastric distress which followed rapid ingestion of food, or after a large meal The sensation of food remaining in the mid-chest was also admitted. Roentgenographic abnormalities were noted in the esophagus in five of the seven who complained of dysphagia; two showed a



FIG. 23 – Roentgenogram of the hand of a patient with systemic scleroderma. Symptoms suggestive of rheumatoid arthritis had been present for two years. There is periarticular swelling of the proximal phalangeal joints and diminution of joint spaces.



[illegible] lowing a swallow of barium by a patient with chronic systemic scleroderma There is dilatation of the esophagus with marked delay in migration of the barium

normal pattern Eight of the patients who denied subjective symptoms revealed abnormalities following ingestion of barium Two patients experienced symptoms of gastrointestinal disturbance but failed to show any roentgenographic evidence of altered motility.

The time of transit of the barium from the pharynx to the stomach was prolonged, and complete emptying sometimes was delayed for as long as thirty minutes (Fig 24) Little or no sluggishness was observed in the upper portion of the esophagus. The lower portion of the esophagus was narrowed in some patients and "gave the impression of resisting dilatation beyond a definitely fixed diameter, although the wall itself did not seem to be rigid" [129] The esophagus was dilated above this area The esophagus appeared narrower than normal throughout the entire course in one patient. The changes described were more marked in the horizontal position, suggesting that the esophagus had lost its normal peristaltic force and that gravity was [illegible] major role [illegible] in cardiospa[illegible] the lower e[illegible] into the stomach appeared at a slow but fairly constant rate The passage of barium from the stomach was delayed because of spasm of the antrum Four of the 18 patients examined had clinical symptoms which suggested obstruction of the small bowel (Figs 25, 26) Changes in the bowel pattern were noted in each patient There was widening of the upper portion with marked delay in emptying Although the changes in the small bowel suggested a paralytic ileus, or a deficiency disease, these might be differentiated Barium may remain in the small intestine for 48 hours after ingestion

Harper [431] observed esophageal changes in each of 14 patients, changes in the small bowel in three, and changes in the colon in eight An asymmetric outline with haustration on one side of the large bowel and diverticula on the opposite wall presented an unusual appearance Gastrointestinal symptoms were mild or absent if the evidence of



FIG 24 —Roer . . . . . . lowing a swallow of barium by a patient with chronic systemic scleroderma There is dilatation of the esophagus with marked delay in migration of the barium

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FIG 25 —Roentgenogram of the upper gastrointestinal tract following a swallow of barium by a patient with acute systemic scleroderma There is minimal dilatation throughout the esophagus with a relatively rigid wall and without any demonstrable peristaltic activity The stomach and the first portion of the duodenum appear normal The second, third and fourth portion of the duodenum and the upper jejunum show segmental dilatation with relatively normal mucosal markings



FIG 26—Roentgenogram of the gastrointestinal tract taken at same examination as in FIG 25 Segmental dilatation of jejunum and ileum is noted



FIG 25—Roentgenogram of the upper gastrointestinal tract fo lowing a swallow of barium by a patient with acute systemic sclerc derma There is minimal dilatation throughout the esophagus with relatively rigid wall and without any demonstrable peristaltic activit The stomach and the first portion of the duodenum appear norma The second, third and fourth portion of the duodenum and the uppe jejunum show segmental dilatation with relatively normal mucosa markings



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Fig 26—Roentgenogram of the gastrointestinal tract taken at same examination as in Fig 25 Segmental dilatation of jejunum and ileum is noted

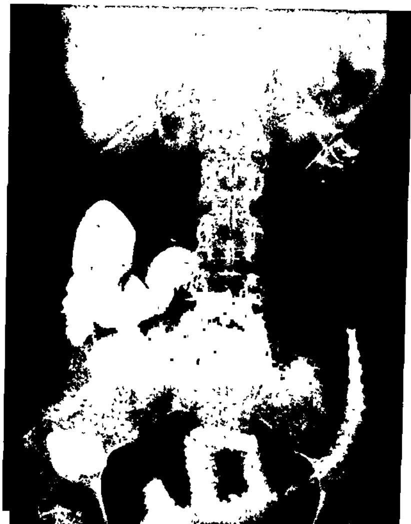


Fig 27 —Roentgenogram of the large bowel following a barium nema of a patient with chronic systemic scleroderma Segmental dilaation is evident.

dysfunction by x-ray was minimal On the other hand, if roentgenographic changes were marked, there was usually a history of alternating constipation and diarrhea Several observers have reported roentgenographic changes in the large bowel (FIG 27) suggestive of ulcerative colitis without involvement of the sigmoid either as determined by roentgenographic examination or by sigmoidoscopy. Cullinan [*410*],

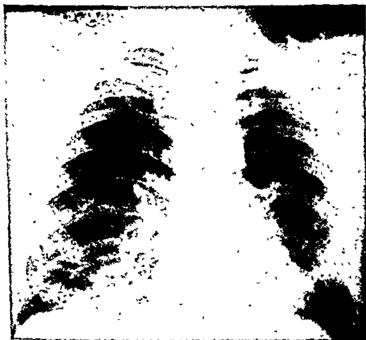


FIG 28 —Roentgenogram of chest of patient with chronic systemic scleroderma *Diffuse pulmonary fibrosis is apparent*

on the other hand, observed a pale, rigid wall of the rectum and lower sigmoid in one patient during sigmoidoscopy A flat plate of the abdomen may show an enlargement of the liver or spleen which may be related to right heart failure in some patients [*400*]

Examination of the chest discloses interstitial fibrosis (FIGS 28, 29) or cyst *formation in a significant percentage of*

patients with scleroderma The process *may begin in th* central portion of the bases. Cysts of varying sizes may de velop, and spontaneous *pneumothorax may be an eventuality* The cases reported by Weiss and associates [*503*] showe



FIG 29 —Roentgenogram of chest of the same patient as in FIG 28, *taken two years later Progression of fibrosis is marked The patient* died a few weeks after this x-ray was taken Post-mortem examination confirmed the diagnosis of systemic scleroderma

findings which suggested bronchiectasis or lipoid pneumonia. Aronsen and Wallerstein [*386*] suggested that cystic changes are demonstrated more readily if the films are overexposed Harper [*131*] has presumed that some of the pulmonary findings are associated with a "spillover" from a malfunctioning esophagus, which results in recurring episodes of



FIG 30 —Roentgenogram of the chest and upper abdomen of a patient with acute systemic scleroderma There is a diffuse interstitial pulmonary fibrosis as well as enlargement of the heart There is blunting of the costophrenic angles It is noted that the stomach is grossly dilated in spite of a nasogastric tube in proper position

localized pneumonitis and pleurisy Undoubtedly such changes occur, but the progressive fibrosis of the lungs is believed to be related to the generalized sclerodermatous process [*458*] and is not secondary to esophageal dysfunction

The cardiac silhouette may be enlarged (FIG 30) Six patients studied by Weiss and associates [*503*] showed a tri-

angular shape without prominence of either left ventricle or left auricle. The silhouette suggested neither *hypertensive nor valvular heart* disease. The combination of the triangular shape and the weak impulses evident upon fluoroscopy may be similar to that observed in myxedematous heart disease or in a pericardial effusion [*431*] Numerous alterations in the electrocardiogram have been noted [*428*] Low voltage, auricular or ventricular premature systoles, auricular fibrillation, gallop rhythm, prolongation of the Q-T interval, left axis deviation, varying degrees of heart block and bundle branch block have been recorded [*450, 503*].

O'Leary and Nomland [*475*] observed the basal metabolic rate to be greater than plus 10 per cent in 17 out of 38 patients. In seven of these there was clinical evidence of hyperthyroidism Hypometabolism was not observed in any instance Electroencephalographic studies were reported on 52 patients by Leinwand and associates [*450*]. Twenty-eight showed significant abnormalities; seven showed minor changes only. The abnormal tracings did not follow any regular pattern but were indicative of alterations in cortical activity. These were attributed either to vascular lesions in the cortex or to alterations of an "undetermined chemical nature"

DIAGNOSIS

The diagnosis should be obvious in the well-developed stage with extensive cutaneous and subcutaneous findings The true nature of the malady in the first weeks or months after onset of symptoms may be masked by clinical findings suggestive of rheumatoid arthritis or Raynaud's syndrome. Malaise, loss of weight, anorexia, low-grade fever and other generalized symptoms suggest something more serious than Raynaud's syndrome but do not help in excluding atypical rheumatoid arthritis. Although most patients will exhibit some evidence of cutaneous involvement of the face or hands, in addition to symptoms of vasospasm, others develop pro-

found skin changes only after systemic symptoms have been present for some time

The diagnosis usually is not difficult following the transition from localized scleroderma, uncomplicated Raynaud's syndrome, or atypical rheumatoid arthritis to systemic scleroderma Cutaneous involvement of the hands and face, especially with hardening and atrophy of the skin, limitation of joint motion, obliteration of the normal cutaneous folds of the hand and face, symptoms of gastrointestinal dysfunction, and pulmonary deficiency should leave little doubt regarding the clinical diagnosis Microscopic changes in the skin and muscle, together with roentgenographic changes in the chest, gastrointestinal tract and skeleton satisfy the several criteria

The differential diagnosis in systemic scleroderma includes acute dermatomyositis, SLE, scleredema, Addison's disease [*478*], hyperthyroidism, myasthenia gravis, malignant hypertension, primary and secondary hyperparathyroidism, acute and chronic glomerulonephritis, carcinoma of the esophagus, excessive vitamin D intake, idiopathic chronic ulcerative colitis, regional ileitis, myositis ossificans, and malnutrition with vitamin deficiency

CLINICAL COURSE

The disease is fatal ultimately, although duration of life following onset of symptoms is extremely variable and unpredictable in most patients There are well-documented instances of patients dying within one year after onset of symptoms [*420*] We have seen a patient recently who lived for only a few weeks after onset of symptoms Post-mortem examination revealed ominous vascular changes in the kidney, which were considered to be the immediate cause of death The disease may persist for two or three decades in exceptional instances Although there is no specific treatment for systemic scleroderma, advances in many phases of medicine are contributing to the prolongation of life in these patients Either renal failure or cardiac failure is responsible

for death when it occurs within the first few years of the malady. Malnutrition and pulmonary complications may be important contributory causes in the chronic cases with a prolonged clinical course

TREATMENT

There is no specific treatment for systemic scleroderma It would be reasonable to assume in such a progressively incapacitating malady that many procedures have been proposed, given a complete or an incomplete therapeutic trial, found to be unsatisfactory, and abandoned. Proper evaluation of specific therapeutic results is handicapped by the tendency of the disease to undergo partial remission without warning and without a recognized cause—a feature of each of the collagen disorders Since the course usually is a prolonged one, every effort should be made to maintain nutrition with a high caloric and a high protein diet, to avoid infections, to maintain as optimistic an outlook as possible, to provide physical therapy for muscle and joint distress, and to institute measures which may delay the development of contractures of the extremities [*393*] Adequate protection against exposure to cold will minimize distress from vasospasm

A number of drugs have been tried in the hope of achieving benefit *Zarafonetis and associates [381] noted* amelioration in seven patients following administration of para-aminobenzoic acid The sclerodermatous areas softened; there was improvement in range of motion as well as a decrease in pigmentation in four patients The experience of Evans and associates [*420*] is quite the contrary Only one of 14 patients was reported to be helped by this drug Vitamin A, nicotinic acid, vitamin B_{12}, vitamin C, and alpha-tocopherol have been used and abandoned as ineffective Slightly encouraging results have been reported from several clinics with vitamin D When doses as large as 300,000 units of vitamin D were given daily, significant improvement was noted [*409*] Improvement in skin changes without effect

upon the general condition was reported by Robles [487] in three patients following large doses of irradiated ergosterol Microscopic examination of the skin before and after treatment showed a decrease of connective tissue proliferation Bernstein and Goldberger [396] reported improvement in one case following administration of dihydrotachysterol (AT-10) Caution should be exercised if large doses of vitamin D or AT-10 are used for more than a few weeks because of possible serious renal complications [409] Other therapeutic agents tried in selected instances with equivocal results include priscolin, glycerol trinitrate, bismuth, procaine, promin, isoniazid, diphenhydramine nitrogen mustard [438], padutin [436], tetracycline, chloramphenicol, antihistiminics, HPC (3-hydroxy-2 phenylcinchoninic), hyaluronidase by iontophoresis [480], artane [486] and typhoid vaccine [449]

The use of hormones in the treatment of systemic scleroderma covers a long period of time Osler [478] discussed the use of dessicated thyroid gland but was not impressed with any clinical gain Oliver and Lerman [476] commented upon the value of thyroid extract and concluded that any benefit could be attributed to an increase in the blood supply rather than to correction of a hypofunctioning thyroid Twenty patients with local or diffuse scleroderma were treated with posterior pituitary extract by these physicians Transient local improvement was noted in some With the availability of testosterone and methyltestosterone these hormones have been tried with varying results [432, 464]

Cortisone, hydrocortisone, prednisone and ACTH are believed to be the hormones of choice at the present time Appreciable benefit has been observed in patients with early mild symptoms as well as in those with more serious findings The patient afflicted with an acute fulminating process receives little or no benefit It is important to appreciate that full therapeutic doses of the adrenal steroids are necessary in order to produce significant relief of symptoms The anti pyretic, euphoric and appetite-stimulating actions of the

adrenal products undoubtedly are responsible for most of the gain Objective evidence concerning inhibition of the diffuse pathologic process is not convincing. Regression to the pretreatment status usually follows cessation of therapy [*423, 442, 443*] Improvement in arthralgia and relief from symptoms due to vasospasm have been reported, but the underlying scleroderma appears to be benefited only slightly. Microscopic examination before and after treatment with cortisone has shown suppression of fibroblastic proliferation. Taubenhaus and Lev [*499*] noted increased esophageal peristalsis as determined by ingestion of barium following steroid therapy. The roentgenographic appearance of the lungs was not altered. An improvement in the microscopic appearance of the skin, except for changes in the blood vessels, was attributed to the administration of cortisone. A decrease in the concentration of gamma globulin has been reported by Bayles [*391*] following steroid therapy.

The difficulty in evaluating steroid therapy may be illustrated by one case of Whittle [*504*]. Placebos were used as a control for cortisone. General mobility was improved and symptoms lessened, irrespective of whether cortisone or the placebo was administered Deaths have been reported while the patients have been on steroids or shortly after discontinuance [*406*] Failure to benefit the acute fulminating type is illustrated by the death in renal failure with exudative phenomena of the pleura and pericardium of the patient reported by Lunseth and associates [*461*] Death in one patient with scleroderma was attributed to prolonged treatment with cortisone [*493*] Post-mortem examination revealed thrombotic ischemic infarctions of the kidney. It was postulated that cortisone accelerated the progress of the preexisting vascular lesions in the kidneys

Surgical attack upon the subcutaneous calcium deposits is not to be recommended generally. Other surgical measures have included extirpation of one or more parathyroid glands, sympathectomy and stellate ganglionectomy [*430*]. Leriche [*452*] reported the results of parathyroidectomy in 13 cases

The operation was based upon the presumption that a disturbance of calcium and phosphorus metabolism is an integral aspect of the disease. Improvement in all but one patient was observed. This procedure has not been generally accepted.

There is some rationale for the removal of periarterial sympathetic nerves [*434*] or of the sympathetic chain, particularly if vasomotor symptoms predominate [*384*]. Sympathectomy is not to be recommended unless it is possible to produce vasodilation and improved blood flow by temporary measures [*441*]. The operation has no merit in patients with advanced stages of the disease who show marked skeletal and cutaneous alterations. Sympathetic ganglionectomy and trunk resection with separation of rami and post-ganglionic fibers interrupt sympathetic pathways which carry efferent as well as afferent stimuli to affected areas of the body. Some relief of symptoms may result from the increased flow of blood to the extremities and from the diminution of smooth muscle spasm. Pain may be relieved by the interruption of afferent sensations.

Evans and associates [*420*] have reported their experience with sympathectomy in 25 patients. It is not surprising to learn that "patients in the edematous or early indurated phases with Raynaud's phenomenon were much more favorable candidates than those in the more advanced stages," nor that "the disease would frequently progress after previous initial improvement." Bilateral extensive thoracic sympathectomies were performed—a procedure possibly with some merit in patients with esophageal and facial involvement. Increased mobility of the face and neck, better mastication and ability to smile have been noted. Progressive hoarseness due to sclerodermatous involvement of the larynx was corrected in one patient. No consistent correlation between improvement in swallowing and roentgenographic findings was reported following sympathectomy in those with esophageal complaints. Lewis [*454*] reported one patient who had undergone four successive sympathectomies,

with temporary improvement after each operation. No improvement in pulmonary symptoms was noted by Evans and associates [*420*] Failure to achieve permanent relief has been attributed to re-establishment of the nervous channels that had been interrupted by surgery. An additional factor, and possibly most important, was the continued progress of the generalized disease A deleterious rather than a beneficial effect of sympathectomy has been the experience of Rothman and Walker [*488*] Cervical sympathectomy was performed by Cullinan [*410*] on six patients without appreciable benefit

Thrombotic Thrombocytopenic Purpura

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) is a term applied to a morbid state in which the basic lesion is vascular rather than thrombotic in spite of the descriptive name. When thrombi occur, their formation may be attributed to the basic vascular lesion. Pathologic examination of affected blood vessels reveals a segmental accumulation of hyaline or acidophilic substance beneath the endothelium in the terminal portions of the arterioles and capillaries. This accumulation protrudes into the lumen and, because of its position in the vascular stream, may be covered by platelets. There is a growing sentiment expressed in medical literature that TTP is a representative of diffuse vascular disease [*512*, *525*, *528*, *531*], hence, a description of this malady is incorporated in this monograph. This decision was made with the full realization that valid objections have been raised to the inclusion of TTP within the concept of collagen disease. It has been presumed that injury to connective tissue in the intima of the vessel results in thrombotic thrombocytopenic purpura, injury within the vessel wall leads to polyarteritis, while perivascular mesenchyme suffers in systemic lupus erythematosus [*512*].

Although the designation, thrombotic thrombocytopenic purpura, is not a correct descriptive appellation, it refers to a clinical entity with characteristic pathologic findings. Allen [*508*] preferred the term "arteriolocapillary thrombonecrosis" initially. This was changed to "thrombocytopenic verrucal angionecrosis," a designation that has

received the blessing of March [527]. The term, thrombotic thrombocytopenic purpura, however, had best be retained at the present time until there is more general agreement regarding a precise descriptive designation [528].

The natural history of TTP includes an acute and a subacute variety. Each appears to be fatal. The acute form often is a dramatic febrile illness characterized by three paramount manifestations: thrombocytopenic purpura, hemolytic anemia and changing neurologic signs. Paradoxically, it has been noted that hemorrhagic symptoms may be mild, despite profound thrombocytopenia. In the subacute form, remissions and exacerbations may appear over a period of several months Its relative rarity exceeds that of the other diseases discussed here However, one case reported in 1925 [529] compares with 10 cases reported in 1952 [537]. The incidence is increasing steadily, mainly because clinical awareness has increased.

HISTORICAL

Credit for the original description of the disease is accorded to Moschowitz [529]. In 1925, he presented the clinical and pathologic findings in a young girl who suffered from a rapidly developing anemia, fever and petechia. Microscopic examination of the terminal arteries showed "thrombi" which were surrounded by cells thought to be fibroblasts Baehr and associates [510] in 1936 described four cases of "an acute febrile anemia and thrombocytopenic purpura with diffuse platelet thromboses of capillaries and arterioles" of the kidneys, heart, adrenals and pancreas It was noted that the endothelial activity in some sections was *out of proportion to the extensive thromboses* and that the thrombi were chromophobic to iron and hemoglobin stains Reference was made to the similarity in the pathologic findings in the blood vessels of the case described by Moschowitz. Marsh [527] has assumed that one or possibly more of the patients suffered from the malady under discussion Friedberg and Gross, [518] at approximately the same time, de-

scribed a case with clinical and pathologic findings that were typical of TTP. Keil [524] is believed to have been the first to suggest that TTP was related to the other collagen diseases, specifically, SLE was noted by name

Altschule [509] reported an example of TTP in 1942 and presumed that damage to the vascular endothelium was responsible for deposition of platelets This is believed to be the first suggestion that a vascular lesion precedes the development of a thrombus. The designation, thrombotic thrombocytopenic purpura, was suggested by Singer, Bronstein and Wile [535] in 1947 A comprehensive review of the disease was published by Singer [534] in 1954 Gore [521] was one of the early investigators to state clearly that the "thrombi" represent hyaline accumulations beneath the endothelium which protrude into the lumen of the vessel The endothelium becomes broken, and platelets in the blood stream become attached as a result of activity of the lesion Thus the primary vascular nature of TTP, rather than intraluminal thrombi was stated

INCIDENCE

Fewer than 100 cases of TTP have been described in current accessible literature Undoubtedly a greater number have been observed and not reported It was believed until recently that females comprised most of the patients This concept has changed since several males have been reported to be afflicted The age of the patients ranges from nine to 69 years A majority are stricken between the ages of ten and 40 years There is no recognized racial predisposition Seven cases have been reported in Negroes [506].

RELATION TO OTHER COLLAGEN DISORDERS

A presumptive diagnosis of rheumatoid arthritis, acute rheumatic fever, or Raynaud's syndrome has been made in isolated examples of TTP, prior to the development of overwhelming symptoms This possibility is greater in patients

with clinical evidence that suggests SLE. Gendel and associates [519] observed one patient with a butterfly rash on the face and a biologic false-positive serologic test. The clinical diagnosis of SLE was refuted by the pathologic findings of TTP The experience of Laszlo and associates [525] was more definitive A 33-year-old female had had symptoms suggestive of rheumatoid arthritis for eight years prior to the terminal events A suspicion of SLE was entertained when she became acutely ill. This was confirmed by the recognition of many LE cells in the peripheral blood. Post-mortem examination revealed "wire loop" lesions in the kidney, "onion skin" lesion in the spleen, fibrinoid degeneration of many of the vessels in the viscera, as well as characteristic endothelial changes of TTP throughout many of the sections studied Other examples of SLE and TTP occurring together have been reported by Barondess [511], Beigelman [512], Gitlow and Goldwork [520] and Symmers and Barrowcliff [538] Nonbacterial verrucous endocarditis, similar to that seen in SLE, has been observed in several instances of TTP [510, 516, 523] Singer and associates [536] reported the development of TTP in a sibling of a patient with SLE One patient with TTP had had discoid lupus for a period of ten years prior to the disseminated process [528] Only one instance of polyarteritis and TTP in the same person was discovered by us in the literature [296]. Most likely, if one instance has been reported, other examples have appeared in clinical practice

ETIOLOGY AND PATHOGENESIS

The etiology is unknown A strong allergic background was revealed by Adelson [506] in a review of 49 cases collected from the literature. Manifestations of allergy included sensitivity to penicillin [519], sulfonamides [517], iodine [515] and angioneurotic edema. The onset of systemic symptoms in several patients has been preceded by an upper respiratory infection March [527] believes that this observation is significant, not from the point of view of viral or

bacterial etiology, but because microorganisms have been implicated as agents which may cause hypersensitivity

PATHOLOGY

Gross examination may show extensive hemorrhages and necrosis throughout the viscera [506] The heart, kidneys and brain appear to be especially vulnerable There may be bloody fluid in each pleural cavity or a fibrinous pleurisy and a fibrinous pericarditis The liver, spleen and lymph nodes usually are enlarged. The brain may show multiple areas of softening [516]

Microscopically, the vessels distributed widely throughout the body show extensive involvement It appears that subendothelial material accumulates, presumably from altered intercellular cement substance, and then protrudes into the lumen of the vessel The endothelial covering is carried along until it breaks and affords a focus for platelet deposition There is some evidence to indicate that intima, media and adventitia sometimes become involved in addition to the endothelium The acidophilic or hyaline material may appear to replace much of the blood vessel wall, and becomes covered secondarily by platelets when exposed to circulating blood The net effects are seen in the histologic sections, multiple aneurysms of small vessels and multiple thromboses The vascular supply of the kidneys, heart, brain, adrenals, gastrointestinal tract, upper respiratory tract and lungs, skeletal muscle, pancreas and spleen, respectively, may be affected Although all of the smaller vessels, arterioles, veins and capillaries may be involved in selected areas of the body, the arteriolocapillary junction is a frequent site for formation of the characteristic intraluminal lesions. The morphologic features consist of amorphous and finely granular material which stains pink with hematoxylin and eosin (Plate XVI, page 8) The occlusive mass is adherent to and continuous with the vessel wall at some point There may be little or no evidence of organization of

the homogeneous masses at the base of the lesion [540] Fibrin has not been demonstrated within the occlusive masses The normal architecture of the vessel wall frequently is replaced by a thinned structure of an aneurysm Absence of elastic and muscle fibers of the vessels in involved areas may be expected The inflammatory phase, visible microscopically in the other collagen diseases, is absent. Possibly the acute fulminating course of TTP results in death before the inflammatory changes have developed. Variations in the severity of the process may be detected in specimens from the same patient.

The heart muscle shows numerous foci of activity, hemorrhages, and early necrosis of muscle fibers [535]. Focal fibrosis may develop if the process is subacute. Nonbacterial verrucous endocarditis has been observed in several patients [510, 516, 519] as noted above Cortical necrosis of the kidney was observed by Comess [513] in one patient. Examination of the bone marrow shows an increased number of megakaryocytes without any evidence of arrest of platelet production Characteristic changes in the capillaries of the bone marrow have been demonstrated [514]. Other pathologic findings include lung abscess, infarction of the myocardium, ulcers in the gastro-intestinal tract, proliferative glomerulitis, cortical hyperplasia of the adrenals, occlusive vascular lesions in the lymph nodes, bilateral adrenal necrosis, nerve cell damage and glial proliferation [521, 539–540] One patient studied by Cooper and associates [514] had a malignant thymoma with regional metastases This is noted because of the incidence of malignant tumors in dermatomyositis.

CLINICAL FINDINGS

The symptoms may be extremely varied, as in the other collagen disorders Fever, malaise, weakness, chilly sensations and nausea may precede any suspicion of a severe systemic disorder Myalgia and arthralgia may be suggestive of a rheumatic process. Weight loss, cough, abdominal pain,

vomiting and cutaneous lesions have been reported Hemorrhagic manifestations include petechia, epistaxis, ecchymosis and purpura in the skin, mucous membranes and conjunctiva; bleeding from the gastrointestinal tract, genitourinary tract and the upper and lower respiratory passages Cardiac complaints are infrequent despite the severity of lesions of the heart observed at post-mortem examination Neurologic complaints are present in a majority of patients and, together with purpuric manifestations, may dominate the clinical findings. Central nervous system involvement [505] may be suggested by headache, confusion, paresthesias, paralysis, convulsions, stupor, delirium and coma A presumptive diagnosis of encephalitis may seem warranted [540] There may also be evidence of spinal cord and peripheral nerve damage

On physical examination, in addition to evidence of bleeding in the skin and mucous membranes, there may be profound pallor, jaundice, lymphadenopathy, an enlarged liver and spleen, hypertension and reflex changes Perhaps 50 per cent of patients show hepatosplenomegaly Examination of the fundi may show retinal hemorrhages, exudates and papilledema [506, 511] The Rumpel-Leede test is positive Obviously this array of manifestations offers little clue to the diagnosis The finding of thrombocytopenia, hemolytic anemia and central nervous system dysfunction in a patient suffering from a fulminating malady should suggest the diagnosis

LABORATORY FINDINGS

Examination of the blood reveals a normocytic normochromic hemolytic anemia Spherocytosis may be seen in addition to polychromatophilia, normoblasts and variation in size and shape of the red cells Reticulocytosis as high as 54 per cent has been reported An increased fecal and urine urobilinogen excretion suggests a hemolytic type of anemia Usually the direct Coombs' test has been negative, though exceptions have been reported [526, 531] The observation that the Coombs' test usually has been negative should not

be taken to imply that an immunologic hemolytic process is not operating Other hemolytic anemias involving extracorpuscular forces are associated with a negative Coombs' test The white blood cells usually are increased in number. A leukemoid reaction may be present terminally [533] The platelets are consistently diminished, although no platelet antibodies have been demonstrated. Gendel and associates [519] reported an exception in the case of a patient with the pathologic findings of TTP, but with the platelet count of 289,000 before death. There is poor clot retraction, decreased prothrombin consumption, and an increased bleeding time The osmotic fragility test usually is normal but may be increased [536] The sedimentation rate is not elevated to the degree that is characteristic of the other maladies described in this monograph The LE cell phenomenon has been negative when investigated, except in one case [525], but several instances of biologic false-positive reactions for syphilis have been reported [514, 519] Urine examination may show albumin, casts and red blood cells [537] Blood in the urine and stool may appear during hemolytic crises The serum bilirubin may be elevated [536]. The albumin-globulin concentrations may be normal, or a reversal may be observed Cephalin flocculation has been reported positive in selected instances Nitrogen retention may appear terminally The spinal fluid may show an increase in proteins and cells Patients have shown severe central nervous system symptoms, however, with essentially normal findings in the spinal fluid [528]

Adelson and associates [506, 507] studied the mechanism of thrombocytopenia and observed a shortened life span of transfused platelets On the other hand, plasma from a patient with TTP did not cause a reduction in the number of thrombocytes in control patients Yet such an observation means only that the platelets disappear, or are used up by the process No vital immunologic implication is associated with this phenomenon No platelet autoagglutinins or iso-

agglutinins were present in two cases studied The evaluation of hemolysis demonstrated no autohemolysins, isohemolysins, autoagglutinins or isoagglutinins Differential agglutination studies as described by Ashby showed an extremely decreased red cell survival time [*506*]

A majority of the cases reported in the literature have undergone a bone marrow examination Usually the marrow is hyperplastic with a normoblastic hyperplasia and a normal or slightly increased number of megakaryocytes Some observers have reported a decrease in platelet formation Singer, Bromstein and Wile [*535*], to the contrary, concluded that the production of platelets was not inhibited Cooper and associates [*514*] have reported an interesting observation in bone marrow aspirate that has been embedded in paraffin Characteristic hyaline changes in blood vessel walls in the marrow were observed with this technic Microscopic examination of lymph modes, skin and muscle usually shows only the characteristic alterations in the blood vessels [*514*, *535*, *537*]

DIAGNOSIS

The clinical diagnosis is being suspected more frequently, even though, admittedly, this is a rare disease The diagnostic triad of hemolytic anemia, thrombocytopenic purpura and neurologic manifestations is highly suggestive A young person acutely ill with purpura and hemolytic anemia should be under suspicion The diagnosis has been made ante-mortem in a minority of cases reported in the literature It is reputed to have been made first by Engel, Scheinker and Humphrey [*516*] in 1947. The diagnosis was made by Meacham and associates [*528*] in one patient from microscopic changes in the spleen that had been removed as a therapeutic procedure The finding of characteristic blood vessel changes by Cooper and associates [*514*] in aspirated bone marrow is the only laboratory procedure that appears hopeful in substantiating a presumptive clinical diagnosis

A muscle and skin biopsy is to be recommended if the bone marrow study does not confirm the diagnosis Positive findings in these tissues have been reported A biologic false-positive test for syphilis may be helpful.

There are several dyscrasias that should be mentioned in considering the differential diagnosis In each instance the general clinical state is less ominous than in TTP Idiopathic thrombocytopenic purpura has few neurologic signs, and when they develop, they are persistent and not transient. Leukopenia rather than a leukemoid blood picture is usual The jaundice in acquired hemolytic anemia is out of proportion to the observed blood loss, the Coombs' test is positive, *and central nervous system manifestations are infrequent* Hereditary spherocytosis seldom is associated with severe thrombopenia and hemorrhagic manifestations A positive family history usually is observed in this malady [*519*]. Paroxysmal nocturnal hemoglobinuria is characterized by a leukopenia, hemoglobinuria and a positive acid fragility test. In this condition, thrombocytopenia is not severe; though central nervous symptoms may be present, they are persistent Polyarteritis, SLE, acute glomerulonephritis, leukemia and subacute bacterial endocarditis have been considered in the differential diagnosis of cases reported in the literature Identifying features of these several entities should not be difficult to establish Certain rickettsial diseases have been discussed as diagnostic possibilities by Tacket and Jones [*539*] Drug sensitivity reactions must be kept in mind, since they may produce hemolysis and thrombocytopenia.

CLINICAL COURSE

The disease has been fatal within six months in most cases that have been reported in the literature. Several have died within a fortnight after the onset of well-developed symptoms and within 48 hours after admission to the hospital On the other hand, the disease has been present with mild clinical findings in a few well-documented cases for more than one year [*506, 537*]

TREATMENT

Supportive measures only are to be recommended The adrenal steroids have not been shown to influence appreciably the course of the disease [506, 523] A splenectomy has been performed in several cases. Meacham and associates [528] observed considerable improvement for three years following this procedure in one patient Muirhead and associates [530] believe that splenectomy has not had a fair trial, because patients subjected to this form of treatment have been in a preterminal stage of the malady These authors suggest that clinical benefit might have been quite different if splenectomy had been carried out immediately following entertainment of the diagnosis On the other hand, the available evidence does not support the general recommendation for splenectomy, and in some instances, purpura may make the risk prohibitive

None of the popular antibiotics used, because of the febrile aspect of TTP, has been shown to have any real value in treatment Red blood or white blood cell transfusions supply only temporary help, but are used in the hope that a remission may occur Platelet transfusions are not practical because of the rapidity with which the platelets are removed from the circulation The effect of any therapeutic agent must be evaluated in relation to the knowledge of the frequency of remissions and exacerbations of TTP

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Thrombotic Thrombocytopenic Purpura

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